



Review Article

Invasive Aspergillosis in Children: Update on Current Guidelines

Athanasia Apsemidou¹, Nikolaos Petridis¹, Timoleon-Achilleas Vyzantiadis² and Athanasios Tragiannidis³.

¹ Department of Internal Medicine, Papanikolaou General Hospital, Thessaloniki, Greece.

² Microbiology Laboratory, Aristotle University of Thessaloniki, Greece.

³ Pediatrics-Pediatric Hematology-Oncology, 2nd Pediatric Department, AHEPA Hospital, Aristotle University of Thessaloniki.

Competing interests: The authors have declared that no competing interests exist.

Abstract. Invasive aspergillosis (IA) is an important cause of infectious morbidity and mortality in immunocompromised paediatric patients. Despite improvements in diagnosis, prevention, and treatment, IA is still associated with high mortality rates. To address this issue, several international societies and organisations have proposed guidelines for the management of IA in the paediatric population. In this article, we review current recommendations of the Infectious Diseases Society of America, the European Conference on Infection in Leukaemia and the European Society of Clinical Microbiology and Infectious Diseases for the management and prevention of IA in children.

Keywords: Invasive aspergillosis, Paediatric, Immunosuppression.

Citation: Apsemidou A., Petridis N., Vyzantiadis T.A., Tragiannidis A. Invasive aspergillosis in children: update on current guidelines. *Mediterr J Hematol Infect Dis* 2018, 10(1): e2018048, DOI: <http://dx.doi.org/10.4084/MJHID.2018.048>

Published: September 1, 2018

Received: April 19, 2018

Accepted: July 15, 2018

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Athanasia Apsemidou. Department of Internal Medicine, Papanikolaou General Hospital, Thessaloniki, Greece. E-mail: sissyaps@gmail.com

Introduction. Invasive fungal infections (IFI) caused by the mould of the genus *Aspergillus* are an important cause of morbidity and mortality in immunocompromised children, mainly including those with cancer or those who had to undergo hematopoietic stem cell transplantation (HSCT).¹⁻⁸ A three- to fourfold increase in the incidence of invasive Aspergillosis infections (IAI) during the past decade has been reported, which is suggested to be correlated with more invasive treatment methods and the survival rate of immunocompromised patients. During 2000, the annual incidence of IAI was 437/100,000 (0.4%) among hospitalized immunosuppressed children in the United States, while almost 75% of the patients had an underlying malignancy.^{2,9-10} This at-risk population for invasive aspergillosis (IA) is comprised mainly of patients with prolonged

granulocytopenia, haematologic malignancies, allogeneic HSCT recipients, solid organ transplantation (SOT) recipients, patients treated with glucocorticosteroids. Patients with refractory or relapsed acute leukemia in the reinduction are at high risk for IA. The highest incidence rates in a single-center study were found in pediatric patients with de novo or recurrent acute myeloid leukemia (AML) (28% each), recurrent acute lymphoblastic leukemia (ALL) (9%), and de novo ALL (2%).^{1-6,11,12}

According to a large contemporary study, *Aspergillus fumigatus* is the predominant isolate, as in adults, followed by *Aspergillus flavus* and *Aspergillus terreus*, while the lungs are the most frequently infected site, followed by disseminated disease.^{1-3,13} Especially in the pediatric population, primary cutaneous aspergillosis has been reported

and associated with a favorable prognosis.^{4,14,15} *A. fumigatus* seems to be the most common species isolated in the pulmonary infections, while *A. flavus* is predominantly found in skin infections.³

Despite improvements in antifungal prevention and treatment, IA is related to high mortality rates, which are historically ranging from 52.5%-85% in children with cancer, while the overall fatality rate of pediatric patients with IA who had to undergo allogeneic HSCT ranges from 45%-80% in different studies.^{3-6,8,16-20} In children with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) IAI increases the mortality rate 5-fold for AML and 14-fold for ALL.² The observation from the literature reveals that the overall mortality before 1990 was 82.8%, while is reported to be 39.5% after it.²¹

In this review article, the International guidelines for the management of Aspergillosis disease published in the last three years are summarized and compared. Among other national and international guidelines in this review are compared the guidelines of the Infectious Diseases Society of America (IDSA), the European Conference on Infection in Leukaemia (ECIL) and the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) - ECCM (European Confederation of Medical Mycology) - ERS (European Respiratory Society) guidelines.^{12,22,23} The methodologies used by the three expert groups are quite similar. IDSA guidelines published in 2016 focus on adults and issue specific recommendations for children because of their different drug dosage and pharmacology, while recommend using the same treatment approach as in adults.¹² Of note, the ECIL group focuses on pediatric patients with cancer and HSCT recipients.²² Additionally, the ECIL group issues guidelines for diagnosis, prevention, and management of invasive opportunistic fungal diseases (IFDs) and not strictly for IA, whereas ESCMID-ECMM-ERS experts group issues guidelines specifically for the prevention, diagnostic procedure, and management of aspergillosis in adults and pediatric population.^{22,23} The strength of recommendation and the quality of evidence vary between the different working groups except for the ECIL group that adopted the grading system suggested by the IDSA for adults, whereas the important differences existing for pediatric patients were considered.²² The IDSA expert group also provides

guidance on how the factors that could increase or decrease the quality of evidence should be weight and regarding the strength of a recommendation if the benefits of following it are likely to outweigh potential harms.¹² Differentiations in methodology, scope and patients populations between these guidelines are shown in **Table 1**.

Diagnosis of IA in Children. Recommendations regarding the diagnosis of IA in children have been proposed by the ECIL, ESCMID-ECMM-ERS and IDSA expert groups.^{12,22,23} All the guidelines recommend that early recognition and rapid initiation of effective treatment are key to the control of the infection and that the diagnosis should be based on the integration of clinical, radiological and microbiological data. Both microscopy and culture should be attempted on specimens received from patients at risk for IA as mandated by clinical findings, although there are difficulties in obtaining the appropriate specimen, the long-time of culturing and the low (50%) sensitivity of the diagnostic value of the culture.^{12,22-30}

Galactomannan (GM) is a heteropolysaccharide, cell-wall component released by all *Aspergillus* spp that can be detected in the serum and bronchoalveolar lavage (BAL) samples by an enzyme immunoassay with high specificity and sensitivity in pediatric patients, although false-positive results can occur for various reasons.³¹⁻⁴⁵ GM testing has a lower sensitivity for use in non-neutropenic patients and those who have received mold-active prophylaxis.^{46,47} Although there is a limited number of studies evaluating the use of GM assay in pediatric patients, the combined sensitivity and specificity of the five pediatric studies that used EORTC/MSG criteria and included adequate information for individual patients were comparable to adults.^{34,36,48-51} Blood GM testing in diagnosing invasive aspergillosis is strongly recommended by the ESCMID-ECMM-ERS group for use in prolonged neutropenic patients with underlying hematological malignancy and for monitoring patients with cancer, while the same recommendations are proposed for children. Additionally, serial screening for GM in blood in neutropenia and HSCT recipients in the absence of mould prophylaxis has a high sensitivity and negative predictive value for IA in a clinical and imaging context. The Further to this, the IDSA and

Table 1. Comparison of the methodology of guidelines for IA in children.

	IDSA	ECIL	ESCMID-ECMM-ERS
Population	Children (prolonged neutropenia HSCT, SOT, corticosteroid use, inherited or acquired immunodeficiency)	Pediatric hematological patients, HSCT recipients	Children (hematological malignancies, solid tumours, HSCT)
Scope	Diagnostic procedures, management of IA	Diagnostic procedures, prevention/treatment of IFDs	Diagnostic procedures, prevention/treatment of IA
Published Evidence search Strength of recommendation	2016 IDSA/SPGC A: good evidence to support a recommendation for or against use B: moderate evidence to support a recommendation for or against use C: poor evidence to support a recommendation for or against us	2014 EBMT/EORTC/ELN/ICHS As IDSA	2017 EFISG A: strongly recommended for use B: moderately recommended for use C: marginally recommended for use D: supports a recommendation against use
Quality of evidence	I: evidence from at least one well-executed randomised trial II: evidence from at least one well-designed non-randomised clinical trial; cohort or case–controlled analytical studies III: evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees	As IDSA	I: evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial) II: evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

ECIL, European Conference on Infection in Leukaemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; HSCT, haematopoietic stem cell transplant; IA, invasive aspergillosis; EORTC, European Organization for Research and Treatment of Cancer; IDSA/SPGC, Infectious Diseases Society of America (IDSA)/Standards and Practice Guidelines Committee (SPGC); EFISG, European Fungal Infection Study Group (EFISG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID); ELN, European Leukemia Network; ICHS, International Immunocompromised Host Society; EBMT, European Group for Bone Marrow Transplantation.

ECIL group strongly recommend the serum and BAL GM as an accurate marker in children with hematologic malignancy and HSCT recipients, but not in SOT recipients and in children who have received mold-active prophylaxis.^{12,22,23,52-69} Finally, a limited amount of data also suggest the usefulness of GM testing in the cerebrospinal fluid (CSF) of children with involvement of the CNS.^{70,71}

The presence of (1→3)-β-D-glucan in serum signifies the presence of fungal invasion but is not specific for *Aspergillus* spp, as it could also be positive in candidiasis, fusariosis, and *Pneumocystis jirovecii* pneumonia.

The β-D-glucan test is not validated yet in children, while higher baseline levels are reported in healthy children, and therefore the cut-off is yet unknown.⁷²⁻⁷⁶ As a result, no evidence-based recommendations can be made for children, only a

proposal for the evaluation of β-D-glucan in high-risk adults with hematological malignancy and allogeneic HSCT.^{12,22,23,77,78}

Regarding the diagnostic value of nucleic acid testing the three groups, ECIL, ESCMID-ECMM-ERS, and IDSA group do not make any recommendation in the pediatric population due to the absence of standardization and validation of the PCR assays results.^{12,22,23} Nevertheless, polymerase chain reaction (PCR) based diagnostic methods in blood or serum are currently evaluated for inclusion as a diagnostic method in the MSG/EORTC consensus group criteria.⁷⁹ Of note, in a recent study in which 71 pediatric patients were evaluated, the sensitivity and specificity of PCR were 80% and 81% respectively.⁸⁰

Typical abnormalities (e.g., halo sign, air crescent sign) on CT-chest as described in adults are less frequent in children in which masses or

infiltrates predominate. Due to the scarcity of evidence in persistently febrile neutropenic children with cancer and proven pulmonary IA, there are no strong recommendations from either of the three groups.^{3,54,81,82} Nevertheless, in high-risk children with febrile neutropenia persistent for more than 96 h or with focal clinical findings, imaging studies such as a CT are moderately recommended by the ECIL group, as they should provide evidence for the initiation of mold-active treatment.²² Regarding the diagnosis of invasive

pulmonary aspergillosis, the IDSA group recommend the performing of bronchoscopy with BAL(A-II), while comorbidities such as severe hypoxemia, bleeding, and platelet transfusion-refractory thrombocytopenia may be considered.¹²

Differences in the strength of the recommendation and the quality of evidence regarding the non-cultural diagnostic methods for diagnosis of IA in children between these groups are shown in **Table 2**.

Table 2. Comparison of the strength of recommendation and quality of evidence in non-culture diagnostic methods for diagnosis of IA in children.

	IDSA	ECIL	ESCMID-ECMM-ERS
GM in serum and BAL and CFS	A-I Diagnostic tool of IA in children with cancer or HSCT ,not recommended for screening in patients in mold-active therapy or prophylaxis, SOT recipients, patients with CGD, could be applied to bronchoscopy specimens from those patients	A-II Prospective monitoring and screening of GM in serum 2/week in children with cancer or HSCT at high risk for IA, not in anti-mould prophylaxis, B-III GM in BAL as a diagnostic tool, B-III GM in CSF	A-I GM in blood Prospective screening for IA in prolonged neutropenia and HSCT recipients not on mold-active prophylaxis, A-II for diagnosis of IA in neutropenic children with hematological malignancy , B-II non-neutropenic, C-II ICU and SOT patients A-II monitoring patients with cancer , GM for diagnosis of IA in BAL, B-II Gm for diagnosis in CSF
β-D-glucan in serum	No specific recommendations and no grading	No specific recommendations and no grading	No specific recommendations and no grading
PCR in blood and serum	A-II PCR assays results considered in conjunction with other diagnostic tests and the clinical context	No specific recommendations and no grading	No specific recommendations and no grading
CT-chest	No specific recommendations and no grading	B-II In high-risk children with febrile neutropenia persistent more than 96 h or with focal clinical findings, B-II typical and non-typical pulmonary infiltrates should prompt further diagnostic work-up and initiation of mould-active antifungal treatment	No specific recommendations and no grading

ECIL, European Conference on Infection in Leukaemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis; GM, galactomannan; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; BAL; bronchoalveolar lavage; SOT, solid organ transplant; CGD; chronic granulomatous disease.

Treatment and Prophylaxis of Invasive Aspergillosis. Although likely to adults, pediatric patients are susceptible to IAIs; relevant differences exist in the epidemiology and underlying conditions, performance and usefulness of diagnostic methods, pharmacology and dosing of systemic antifungal agents, and the availability of evidence generated by interventional phase III

studies. Recommendations for paediatric patients are based on efficacy in phase II and III trials in adults, the availability of paediatric pharmacokinetic data, safety data, supportive efficacy data and regulatory approval.^{22,23} For diagnostic interventions, referenced above, the ECIL group used the adult data as supportive and not as major evidence for useful performance in

children.²² Therapeutic drug monitoring (TDM) is recommended when mould-active azoles are used as prophylaxis or treatment in children, due to the much higher rates of drug elimination and pharmacokinetic variability.^{12,22,23, 83,84}

Primary prophylaxis. Guidelines for the prevention of IA in children are released only by the ESCMID-ECMM-ERS and ECIL experts group. As a general principle, these guidelines recommend the use of antifungal agents as primary prophylaxis in pediatric patients at 'high risk' for developing IA. High risk populations include children with de novo or recurrent leukaemia (AML, ALL), bone marrow failure syndromes with profound and prolonged neutropenia (MDS, aplastic anaemia), allo-HSCT recipients, patients with chronic granulomatous disease and those undergoing lung transplantation.^{85,86} Additionally, the local epidemiology should be considered when designing an appropriate institutional prophylaxis strategy.⁸⁷

Two randomised studies of antifungal prophylaxis compared micafungin and voriconazole, respectively, to fluconazole in the setting of allogeneic HSCT, while paediatric patients were making up about 10% of all enrolled participants. Thus, these two studies provided important randomised safety data for micafungin and voriconazole.^{88,89} Further to this, a large number of retrospective and prospective studies have been done with various mould-active and mould non-active agents.^{90,91} Due to the scarcity of paediatric data, recommendations for lung and liver transplant patients correspond to those made for adults.^{85,86}

ESCMID-ECMM-ERS guidelines strongly recommend (A-II) voriconazole (>2 years, supported by HSCT trials and studies) and posaconazole (>13 years, supported by pediatric data) plus TDM as a prophylaxis for allo-HSCT recipients, in the pre or the post-engraftment phase or with graft versus host disease (GvHD) or with augmented immunosuppression, in high risk paediatric patients with de novo or recurrent leukaemia, with bone marrow failure syndromes with prolonged and severe neutropenia.^{23,92-111} In addition to this, this expert group strongly recommends itraconazole with TDM (approved EU only for patients older than 18 years) in allo-HSCT recipients in the pre-engraftment phase, in

high-risk patients with de novo or recurrent leukaemia, with bone marrow failure syndromes with neutropenia. Whereas, there is moderate evidence for recommendation of this agent in allo-HSCT recipients in post-engraftment phase, with GvHD and in augmented immunosuppression.^{23,112-123} Liposomal Amphotericin B is not approved for prophylaxis, only as an alternative agent in case of triazoles are not tolerated or contra-indicated.^{23,124-130} Further to this, there is no definite evidence for the prophylactic efficacy of micafungin against *Aspergillus* spp, only as an alternative agent in the same cases as above.^{23,131-135} Liposomal Amphotericin B and micafungin have a low quality of evidence for recommendation in allo-HSCT recipients in the post-engraftment phase, with GvHD and in augmented immunosuppression(B-III).²³ Finally, the ESCMID-ECMM-ERS group suggests as a prophylactic strategy for patients with CGD the use of itraconazole and posaconazole with TDM (both not approved in EU for patients <18 years, although for posaconazole safety data exist for children \geq four years, but not yet approved).^{23,97-100,118-123,136,137}

ECIL guidelines suggest three different group of pediatric patients: a) allogeneic HSCT recipients without GVHD b) allogeneic HSCT recipients with GVHD and c) patients with de novo or recurrent leukaemia.

In the first group the ECIL recommends the use of antifungal agents as prophylaxis during the granulocytopenic phase until engraftment (B-II) and after the engraftment in the absence of GvHD until discontinuation of immunosuppression (no grading), including moderate recommendation of voriconazole (children aged >2 years, supported by pharmacokinetic, safety, and efficacy data in paediatric patients) and itraconazole (not approved in children aged <18 years, also supported by pharmacokinetic, safety, and efficacy data in paediatric patients).^{22,110,111,123} Liposomal amphotericin B, as also the ESCMID-ECMM-ERS guidelines suggested, is not approved for prophylaxis of IA. It is approved as an alternative option for patients who do not tolerate triazoles or have contraindications to them (supported by pharmacokinetic, safety, and efficacy data in paediatric patients), while aerosolised liposomal amphotericin B is not either approved for prevention, due to the unknown of the appropriate

dosage schedule in children <18 years.^{22,23,138-140} Finally, regarding posaconazole there is no grading in the ECIL group guidelines because of the limited pharmacokinetic data in children aged ≥ 13 years, in contrast to the ESCMID-ECMM-ERS guidelines which strongly recommend it with TDM for children >13 years.^{22,23,141}

In the second group, in the presence of GvHD treated with augmented immunosuppressive agents (including glucocorticosteroids or anti-inflammatory antibodies), prevention against IAIs is recommended (A-II) by the ECIL guidelines.²² The recommended options are: posaconazole plus TDM for patients aged >13 years (B-I), voriconazole plus TDM for patients aged >2 years (B-I), whereas the ESCMID-ECMM-ERS groups strongly recommend these agents.^{22,23} Additionally, itraconazole plus TDM is also recommended (C-II) for this group of patients. Other options may include intravenous liposomal amphotericin B and micafungin (no grading).²²

Finally, in the third group suggested by the ECIL guidelines, specifically in high-risk patients with de-novo or recurrent acute leukaemia, primary prophylaxis against *Aspergillus* spp should be considered (B-II). The prevention may include itraconazole with TDM (B-I, in children aged ≥ 2 years), although it is not approved for children <18 years, posaconazole plus TDM in patients aged 13 years or older (B-I) and intravenous liposomal amphotericin B (B-II) as an alternative option for patients who do not tolerate triazoles or have contraindications to them. Other possible options include aerosolised liposomal amphotericin B, micafungin, and voriconazole with TDM (no grading because of inferences for efficacy from studies in the HSCT recipients).²² The concomitant use of itraconazole, posaconazole, and voriconazole with vincristine and other anticancer agents should be carefully considered.^{114,138,142,143}

Guidelines for the prevention of IA in children are not released by the IDSA group.¹²

The strength of recommendation, the quality of evidence, the indication and the dosage of the antifungal agents recommended as primary prophylaxis by the two expert groups are shown in **Table 3**.

Secondary prophylaxis. There are a limited number of studies about the term secondary antifungal chemoprophylaxis, but the available

data suggest an IFD relapse rate of 30–50% in leukemia or allogeneic HSCT settings.¹⁴⁰ Data in paediatric patients are limited to a prospective study, which evaluated 11 adolescents with acute leukaemia and a history of antecedent possible or probable IA who received intravenous liposomal amphotericin B followed by oral voriconazole during and after allogeneic HSCT. In the absence of GvHD, two breakthrough infections occurred that were correlated with recurrent leukaemia and refractory graft failure.¹⁴⁴

On the basis of these data and other existing data from adults, secondary antifungal prophylaxis or continued antifungal treatment is recommended by the ECIL guidelines, targeted against the previous *Aspergillus* species, for as long as the patient is neutropenic or immunosuppressed (A-II). [22,145] Nevertheless, no recommendations about the duration of therapy and the extent of patient's response before the continuation of anticancer regimens or initiation of the treatment for allogeneic HSCT could be made by the ECIL group due to the lack of data (no grading).²²

The ESCMID-ECMM-ERS group also proposes that secondary prophylaxis to prevent recurrence of IA in children when risk factors are persisting should consist of an antifungal agent targeted at the previous *Aspergillus* species which caused the first episode.²³

The IDSA guidelines for the secondary prevention of IA in children are the same as for adults. For patients with successfully treated pulmonary aspergillosis who require subsequent immunosuppression, secondary prophylaxis is recommended to prevent recurrence (A-II).¹²

Targeted (first-line) treatment of IA in children. Despite improvements in diagnosis, prevention, and treatment, IA is still associated with high mortality rates among children.^{6,146,147} In the Children's Cancer Group (CCG) Phase III AML chemotherapy trial CCG 2961, the incidence of IFIs in children with AML was 13% per treatment phase and almost one-third of the documented IFI were caused by *Aspergillus* spp and the mortality rate of IA ranged from 15% to 57%, depending on the phase of chemotherapy.¹⁴⁸ A survey performed in the US documented the annual incidence of IA in children to be was 0.4%, while in the US 2000 Kids' Inpatient Database, the fatality rate for children with cancer and IA (21%) at first discharge was much greater than that in children

Table 3. Comparison of recommendations on primary prophylaxis from IA in children.

	ECIL	ESCMID-ECMM-ERS	Dosage (by ECIL)/comments
Voriconazole Indication	B-I for patients >2 years Allo-HSCT with or without GVHD No grading De-novo or recurrent leukaemias	A-III for children >2 years Allo-HSCT recipients, pre and post engraftment phase, GvHD and augmented immunosuppression, high-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged neutropenia	Children aged 2–12 years or aged 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally, children aged ≥15 years or aged 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally plus TDM, not approved <2 years
Itraconazole Indication	B-I for children ≥2 years Allo-HSCT without GVHD C-II for children ≥2 years Allo-HSCT with GVHD B-I for children ≥2 years De-novo or recurrent leukaemias	A-III for patients >18 years Allo-HSCT recipients, pre engraftment phase, high-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged neutropenia B-III for patients >18 years Allo-HSCT recipients in post-engraftment phase, GvHD and augmented immunosuppression A-II for patients >18 years CGD patients	5 mg/kg per day orally (in children aged ≥2 years) in two divided doses plus TDM, not approved EU < 18 years
Posaconazole Indication	No grading for children >13 years Allogeneic HSCT without GVHD B-I for children >13 years Allogeneic HSCT with GVHD B-I for children >13 years De-novo or recurrent leukaemias	A-III for children >13 years Allo-HSCT recipients, pre and post engraftment phase, GvHD and augmented immunosuppression, high-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged neutropenia A-III for children >13 years CGD patients	600 mg per day orally in three divided doses plus TDM, in children aged ≥13 years
Liposomal AmB Indication	C-III Allo-HSCT without GVHD, No grading Allo-HSCT with GVHD B-II De-novo or recurrent leukaemias	B-III Allo-HSCT recipients, pre engraftment phase, high-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged neutropenia B-III Allo-HSCT recipients in post-engraftment phase, GvHD and augmented immunosuppression	1 mg/kg intravenously every other day or 2.5 mg/kg intravenously twice weekly, not approved for prophylaxis, alternative if triazoles are not tolerated / contra-indicated
Micafungin Indication	C-I Allo-HSCT without GVHD, No grading Allo-HSCT with GVHD, No grading De-novo or recurrent leukaemias	B-III Allo-HSCT recipients, pre engraftment phase, high-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged neutropenia B-III Allo-HSCT recipients in post-engraftment phase, GvHD and augmented immunosuppression	1 mg/kg per day (in children weighing ≥50 kg, 50 mg) intravenously in one dose, no definite evidence for prophylactic efficacy against <i>Aspergillus</i> spp. , alternative if triazoles are not tolerated or contraindicated
Aerosolised liposomal AmB Indication	No grading Allo-HSCT without GVHD, De-novo or recurrent leukaemias		12.5 mg on 2 consecutive days per week, Targeted against pulmonary mould infections; non-approved route of administration; appropriate doses and dosage schedule unknown in children aged <18 years

ECIL, European Conference on Infection in Leukaemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis; CGD; chronic granulomatous disease, GVHD, graft versus host disease, t: transferred evidence (i.e. results from different patients' cohorts, or similar immune-status situation)

with malignancy but no IA (1%).^{2,9-10}

The most recent guidelines for the treatment of IA in children were released by the ECIL in 2014, the IDSA in 2016 and the ESCMID-ECMM-ERS in 2017. Although no consistency in the three guidelines is found, in principle voriconazole, liposomal amphotericin B, and caspofungin are proposed as drugs of choice.^{12,22,23}

All of the three expert groups propose that general management principles of IA might include prompt initiation of antifungal treatment, control of predisposing conditions (e.g., reduction or discontinuation of corticosteroids in immunosuppressed patients, colony-stimulating factors in granulocytopenic patients), and surgical interventions on a case by case basis using a multidisciplinary approach. Granulocyte transfusions might be considered in patients with profound and prolonged granulocytopenia. A thorough evaluation of further sites of infection, particularly the CNS, should be included. The optimal duration of therapy is not defined but determined by the resolution of all signs and symptoms and reversal of the underlying deficit in host defenses.^{12, 22, 23,139,140}

The IDSA guidelines propose that in the treatment of IA in children the same recommended therapies as in adult patients should be used with a different dosing.(A-I)¹² This expert group favour the use of voriconazole (approved for patients 12 years and older) also for children by evaluating substantial pharmacokinetic data and experience.¹⁰⁴ The recommended pediatric dosing is higher than for adults. Reduced voriconazole levels may be observed with oral administration.^{12,84,105,149} In addition to this, IDSA groups recommend the liposomal amphotericin B(A-II) with the same dosing as in adults and the posaconazole for children>13 years for both the oral suspension and tablet and for older than 18 years the intravenous formulation. Further to this, it suggests the use of caspofungin for children three months and older and micafungin for children four months and older.^{12,133,150} The echinocandins are strongly recommended to be avoided as a primary treatment (A-II), while the combination with voriconazole may be considered in selected patients(C-II). Of note, anidulafungin is not FDA approved for children.^{12,151-153} Finally, the expert group recommends that treatment of invasive pulmonary aspergillosis need to be continued for a minimum of 6–12 weeks,

dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement (A-III).

The recently published ESCMID-ECMM-ERS guidelines also favour the use of voriconazole (A-II) as the first line agent to treat IA in paediatric patients aged>2 years.^{23,84,104-107,110,111,149,154-159} This experts group gives a more moderate recommendation for the use of Liposomal Amphotericin B (B-II) due to relatively limited clinical data for comparison to voriconazole.^{23,128,130,160-163} Finally, for caspofungin, the ESCMID-ECMM-ERS guidelines give a weak recommendation(C-II) since the study has been prematurely stopped because of low accrual.^{23,150,164-173} All the recommendations of the expert group are referring to pediatric patients with cancer, bone marrow failure syndromes, CGD and to HSCT and SOT recipients.²³

The recommendations of the ECIL group are generally based on dose finding studies and phase III clinical trials. The group gives a strong recommendation for the use of intravenous voriconazole with TDM, based on the pivotal phase 3 trial in adults (A-I; restricted to patients aged ≥2 years). The voriconazole is suggested as a treatment of choice for infections involving the CNS. The drug dosage for children aged 2<12 years or 12–14 years and weighing <50 kg is 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally, while for children aged ≥15 years or 12–14 years and weighing ≥50 kg is 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally plus TDM.^{22,110,111,140} In addition to this, they give a somewhat weaker B-I recommendation for liposomal amphotericin B (3 mg/kg per day intravenously in one dose), due to the fact that the pivotal phase 3 trial was a comparison between two different dose strategies and not a comparison with the reference agent voriconazole. Further to this, they give a moderate recommendation to amphotericin B lipid complex (B-II) with a dosage of 5 mg/kg per day intravenously in one dose. Based on the available data of the randomised, comparative clinical trial the ECIL group suggests no general superiority of combination therapy of voriconazole plus anidulafungin for primary treatment of IA (C-III).^{22,140,174}

Comparison of the strength of recommendation, the quality of evidence of the first line antifungal

Table 4. Comparison of the strength of recommendation and quality of evidence in first line agents for targeted treatment of IA in children.

	IDSA	ECIL	ESCMID-ECMM-ERS
Voriconazole	A-I	A-I	A-II
Liposomal amphotericin B	(A-II)	B-I	B-II
Caspofungin	(C-II)	A-II(considered from this group as a second line agent)	C-II
Amphotericin B lipid complex	No grading	B-II	Not considered as a first-line agent
Antifungal combination therapy	C-II	C-II	Not considered as first-line treatment

ECIL, European Conference on Infection in Leukaemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IA, invasive aspergillosis.

agents for IA in children between the three expert groups is shown in **Table 4**.

Second-line and resistant Aspergillus spp treatment of IA in children. Second-line treatment refers to antifungal treatment in patients with response failure or those with intolerance to the initial treatment.¹⁷⁵

The ECIL group generally suggests that a switch in class might be considered when antifungal treatment is changed for refractory disease (no grading). The group recommends as a second-line treatment liposomal amphotericin B in amphotericin-B-naive patients based on data from the pivotal first-line phase 3 trial (B-I), and voriconazole with TDM in voriconazole-naive patients based on data from the pivotal first-line phase 3 trial and a second-line phase 2 trial (A-I; restricted to children aged ≥ 2 years), respectively.^{22,110,111,140} Other options approved in pediatric patients include amphotericin B lipid complex (B-II) and caspofungin (A-II, dosage: 50 mg/m² per day intravenously in one dose, 70 mg/m² on day 1 loading dose).¹⁸ Regarding the combination therapy, a small phase 2 study, a retrospective cohort study and results from one not fully published phase 3 first-line trial demonstrate that there are no differences in the primary endpoint.^{152,153,170,176} Only a weak recommendation is made by the ECIL group about the combination therapy with either voriconazole or amphotericin B with an echinocandin for

salvage treatment(C-II). Of note, although there is a scarcity of relevant data, the ECIL group recommends a switch in class in patients with breakthrough infections on antifungal prophylaxis or empirical therapy (no grading).

According to ESCMID-ECMM-ERS guidelines, liposomal amphotericin B represents an alternative to voriconazole as first-line treatment of IA in areas or institutions with a high prevalence of azole-resistant *A. fumigatus*. MIC-testing is recommended for all clinically relevant *Aspergillus* isolates or if grown in patients previously exposed to or on antifungal therapy. Isavuconazole is strongly recommended in IA due to amphotericin B resistant species only in the adult population and has not yet been approved for children. A switch to a different class of antifungals is recommended by this expert group for salvage therapy and breakthrough infections.^{23,177-189}

Guidelines by the IDSA group for the second line treatment of IA in children are the same as for adults.¹² The group recommends as a general strategy for salvage therapy, after excluding the emergence of a new pathogen, a switch to a different class of antifungal agent or the use of an alternative agent with a nonoverlapping side-effect profile, a taper or reversal of underlying immunosuppression when feasible, and a surgical resection of necrotic lesions in selected cases (A-III).¹² The options include lipid formulations of AmB, micafungin, caspofungin, posaconazole, or itraconazole (A-II), or combination of antifungal agents from different classes other than those in the initial regimen (C-II).^{12,153,190-193}

Empirical and preemptive (diagnostic-driven) treatment for IA. Empirical treatment for IA is recommended according to the ECIL guidelines in granulocytopenic children with acute leukaemia/allogeneic HSCT after four days of fever of unclear etiology that is unresponsive to broad-spectrum antibacterial agents, and it should be continued until resolution of granulocytopenia in the absence of suspected or documented IFIs (B-II). The ECIL additionally suggests that empirical antifungal therapy might be considered in individual persistently febrile children with low-risk disorders and profound and prolonged granulocytopenia and severe mucosal damage (no grading).¹⁸ Both the ECIL and ESCMID-ECMM-ERS guidelines favour the use of liposomal

amphotericin and caspofungin (A-I) based on large randomised clinical trials comparing the caspofungin versus liposomal amphotericin b and the different formulations of amphotericin b for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia.^{22,23,194-196}

The similar treatment approach is proposed by the ECIL group in those granulocytopenic patients who develop a recurrent fever after afebrile period upon the initiation of broad-spectrum antibacterial agents (no grading).¹⁸ According to the ECIL guidelines, a switch to a different class of mould-active antifungal agents and the initiation of either caspofungin or liposomal amphotericin B for empirical therapy in patients receiving antifungal prophylaxis without mould activity need to be considered (no grading).²²

The intention of pre-emptive antifungal treatment, which uses clinical, usually non-culture-based microbiological and radiographic data to establish whether or not to initiate antifungal therapy in granulocytopenic patients, is to reduce the exposure to unnecessary antifungal therapy. The usefulness of this strategy has been shown in adults, and it has been established as an alternative option to the empirical treatment.¹⁹¹⁻¹⁹⁵

Although there is a lack of data assessing the paediatric population, the ECIL group suggests that pre-emptive approach as a strategy in children (no grading) with the prerequisite of rapid performance of pulmonary CT imaging, GM testing and the availability to undertake bronchoscopies with BAL.²² According to the ESCMID-ECMM-ERS guidelines, treatment recommendations for a diagnostic-driven strategy correspond to those made for targeted treatment.^{23,197-201} Guidelines for empirical and the diagnostic driven therapy of IA in children are not released by the IDSA group.¹²

Conclusions. Although differences are found in pediatric guidelines for the prevention of IA between various societies, general treatment recommendations suggest the prompt initiation of

antifungal treatment, control of predisposing conditions and surgical interventions on a case by case basis using a multidisciplinary approach. The recommendations for treatment favour the use of voriconazole, the lipid formulations of amphotericin B, caspofungin and a combination of antifungal agents. Voriconazole is strongly recommended by the three expert groups like the drug of choice although it should be replaced by liposomal amphotericin B as first-line treatment of IA in areas or institutions with a high prevalence of azole-resistant *A. fumigatus*, according to the recent ESCMID-ECMM-ERS guidelines. Lipid formulations of amphotericin B seem to offer additional treatment options for first line treatment of IA in children. Caspofungin although considered by the ESCMID-ECMM-ERS and IDSA guidelines as a first-line agent, has a weak recommendation due to the premature cessation of a relevant study. Finally, regarding the combination of voriconazole plus anidulafungin, the ECIL group suggests no general superiority, based on the available data of the randomised, comparative clinical trial, while the IDSA group recommend it for selected patients.

IDSA guidelines published in 2016 focus on adults and issue specific recommendations for children while recommend using the same treatment approach as in adults.¹² The ECIL group focuses on pediatric patients with cancer and HSCT recipients.²² Additionally, the ECIL group releases guidelines for diagnosis, prevention, and management of invasive opportunistic fungal diseases (IFDs) and not strictly for IA, whereas ESCMID-ECMM-ERS experts group issue guidelines for the prevention, diagnostic procedure and management of aspergillosis in adults and pediatric population.^{22,23} Despite the usefulness of the above guidelines in the prevention, diagnosis and treatment of IA, guidelines focused on pediatric IA need to be issued considering the high mortality rate of the disease in children.

References:

1. Tragiannidis A, Roilides E, Walsh TJ and Groll AH. Invasive aspergillosis in children with acquired immunodeficiencies. Clin Infect Dis. 2012; 54: 258-256. <https://doi.org/10.1093/cid/cir786> PMID:22075793
2. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics 2006; 117: 711-716. <https://doi.org/10.1542/peds.2005-1161> PMID:16533892
3. Burgos A, Zaoutis TE, Dvorak CC, Hoffman JA, Knapp KM, Nania JJ, Prasad P, Steinbach WJ. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics 2008; 121: 1286-1294. <https://doi.org/10.1542/peds.2007-2117> PMID:18450871
4. 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. <https://doi.org/10.1097/00006454-199308000-00009> PMID:8414781
5. Abbasi S, Shenep JL, Hughes WT, Flynn PM. Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis* 1999; 29:1210-1219. <https://doi.org/10.1086/313445> PMID:10524965
 6. Groll AH, Kurz M, Schneider W, Witt V, Schmidt H, Schneider M, Schwabe D. Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. *Mycoses*. 1999; 42: 431-442. <https://doi.org/10.1046/j.1439-0507.1999.00496.x> PMID:10546484
 7. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; 32: 358-366. <https://doi.org/10.1086/318483> PMID:11170942
 8. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S, Herwaldt LA, Kauffman CA, Knapp K, Lyon GM, Morrison VA, Papanicolaou G, Patterson TF, Perl TM, Schuster MG, Walker R, Wannemuehler KA, Wingard JR, Chiller TM, Pappas PG. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis* 2010; 50: 1091-1100. <https://doi.org/10.1086/651263> PMID:20218877
 9. Steinbach WJ. Epidemiology of Invasive Fungal Infections in Neonates and Children. *Clin Microbiol Infect*. 2010 ;16: 1321-1327. <https://doi.org/10.1111/j.1469-0691.2010.03288.x> PMID:20840541
 10. Segal BH. Aspergillosis. *N Engl J Med* 2009; 360: 1870-1884. doi: 10.1056/NEJMra0808853. <https://doi.org/10.1056/NEJMra0808853>
 11. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984; 100:345-51. <https://doi.org/10.7326/0003-4819-100-3-345> PMID:6696356
 12. Thomas F, Patterson, George R, Thompson III, David W, Denning, Jay A, Fishman, Susan Hadley, Raoul Herbrecht, , Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016. 15; 63(4): e1-e60.
 13. Walsh TJ, Gonzalez C, Lyman CA, Chanock SJ, Pizzo P. Invasive fungal infections in children: recent advances in diagnosis and treatment. *Adv Pediatr Infect Dis* 1996; 11: 187-290. PMID:8718464
 14. Kerl K, Koch B, Fegeler W, Rossig C, Ehler K, Groll AH. Catheter-associated aspergillosis of the chest wall following allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2011; 13: 182-185. <https://doi.org/10.1111/j.1399-3062.2010.00559.x> PMID:20738831
 15. Allo MD, Miller J, Townsend T, Tan C. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. *N Engl J Med* 1987; 317: 1105-1108. <https://doi.org/10.1056/NEJM198710293171802> PMID:3657878
 16. Lin SJ, Schranz J, Teutsch SM: Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; 32: 358-366 <https://doi.org/10.1086/318483> PMID:11170942
 17. 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. <https://doi.org/10.1038/sj.bmt.1702654> PMID:11100280
 18. Benjamin DK Jr., 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. <https://doi.org/10.1097/00006454-200203000-00013>
 19. Crassard N, Hadden H, Pondarré C, Hadden R, Galambrun C, Piens MA, Pracros JP, Souillet G, Basset T, Berthier JC, Philippe N, Bertrand Y Invasive aspergillosis and allogeneic hematopoietic stem cell transplantation in children: a 15-year experience. *Transpl Infect Dis* 2008;10:177-183 <https://doi.org/10.1111/j.1399-3062.2008.00304.x> PMID:18331389
 20. Castagnola E, Faraci M, Moroni C, R Bandettini, C Granata, S Caruso, F Bagnasco, I Cavaglia, M Malgorzata, E Furfaro, A R Natalizia, V de Fazio, G Morreale, E Lanino, R Haupt, G Dini & C Viscoli. Invasive mycoses in children receiving hemopoietic SCT. *Bone Marrow Transplant* 2008;41 Suppl 2:S107-11 <https://doi.org/10.1038/bmt.2008.67> PMID:18545231
 21. Dotis J, Iosifidis E, Roilides E. Central nervous system aspergillosis in children: a systematic review of reported cases. *Int J Infect Dis* 2007; 11: 381-393 <https://doi.org/10.1016/j.ijid.2007.01.013> PMID:17509921
 22. Andreas H Groll, Elio Castagnola, Simone Cesaro, Jean-Hugues Dalle, Dan Engelhard, William Hope, Emmanuel Roilides, Jan Styczynski, Adilia Warris, Thomas Lehrnbecher. 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: 327-340 [https://doi.org/10.1016/S1470-2045\(14\)70017-8](https://doi.org/10.1016/S1470-2045(14)70017-8)
 23. Ullmann AJ, Aguado JM, Arikian-Akdagli S, Denning D, Groll A, Lagrou K, C. Lass-Flör, R.E. Lewis, P. Muno, P.E. Verweij, A. Warris, F. Ader, M. Akova, M.C. Arendrup, R.A. Barnes, C. Beigelman-Aubry, S. Blot, E. Bouza, R.J.M. Brüggemann, D. Buchheidt, J. Cadranel, E. Castagnola, A. Chakrabarti, M. Cuenca-Estrella, G. Dimopoulos, J. Fortun, J.-P. Gangneux, J. Garbino, W.J. Heinz, R. Herbrecht, C.P. Heussel, C.C. Kibbler, N. Klimko, B.J. Kullberg, C. Lange, T. Lehrnbecher, J. Löffler, O. Lortholary, J. Maertens, O. Marchetti, J.F. Meis, L. Pagano, P. Ribaud, M. Richardson, E. Roilides, M. Ruhnke, M. Sanguinetti, D.C. Sheppard, J. Sinkó, A. Skiada, M.J.G.T. Vehreschild, C. Viscoli, O.A. Cornel. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS-ECMM-ERS guideline. *Clinical Microbiology and Infection*. 2018. <https://doi.org/10.1016/j.cmi.2018.01.002>.
 24. Fraczek MG, Kirwan MB, Moore CB, Morris J, Denning DW, Richardson MD. Volume dependency for culture of fungi from respiratory secretions and increased sensitivity of aspergillus quantitative per. *Mycoses*. 2014; 57: 69-78. <https://doi.org/10.1111/myc.12103> PMID:23786547
 25. Dornbusch HJ, Manzoni P, Roilides E, Walsh TJ, Groll AH. Invasive fungal infections in children. *Pediatr Infect Dis J* 2009; 28: 734-737. <https://doi.org/10.1097/INF.0b013e3181b076b1> PMID:19633517
 26. Dornbusch HJ, Groll A, Walsh TJ. Diagnosis of invasive fungal infections in immunocompromised children. *Clin Microbiol Infect* 2010; 16: 1328-1334. <https://doi.org/10.1111/j.1469-0691.2010.03336.x> PMID:20678175
 27. Roilides E. Early diagnosis of invasive aspergillosis in infants and children. *Med Mycol* 2006; 44: 199-205 <https://doi.org/10.1080/13693780600810057>
 28. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev* 2011; 24:247-280 <https://doi.org/10.1128/CMR.00053-10> PMID:21482725 PMID:PMC3122495
 29. Vyzantiadis TA, Johnson EM, Kibbler CC. From the patient to the clinical mycology laboratory: how can we optimise microscopy and culture methods for mould identification? *J Clin Pathol* 2012; 65:475-483 <https://doi.org/10.1136/jclinpath-2011-200500> PMID:22308268
 30. Barton RC. Laboratory diagnosis of invasive aspergillosis: from diagnosis to prediction of outcome. *Scientifica* 2013; 2013:459405. <https://doi.org/10.1155/2013/459405> PMID:24278780 PMID:PMC3820361
 31. Lehrnbecher T, Phillips R, Alexander S, Alexander S, Ammann RA, Beauchemin M, Carlesse F, Groll AH, Haeusler GM, Santolaya M, Steinbach WJ, Castagnola E, Davis BL, Dupuis LL, Gaur AH, Tissing WJE, Zaoutis T, Phillips R, Sung L and the International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/ or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol* 2012; 30: 4427-4438. <https://doi.org/10.1200/JCO.2012.42.7161> PMID:22987086
 32. Groll AH, Tragiannidis A. Recent advances in antifungal prevention and treatment. *Semin Hematol* 2009; 46: 212-229. <https://doi.org/10.1053/j.seminhematol.2009.03.003> PMID:19549575
 33. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. *Clin Infect Dis*. 2006; 42: 1417-1427. <https://doi.org/10.1086/503427> PMID:16619154
 34. Hovi L, Saxen H, Saarinen-Pihkala UM, Vettenranta K, Meri T, Richardson M. Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. *Pediatr Blood Cancer*. 2007; 48: 28-34. <https://doi.org/10.1002/pbc.20717> PMID:16395687
 35. Steinbach WJ, Addison RM, McLaughlin L, Gerrald Q, Martin PL,

- Driscoll T, Bentsen C, Perfect JR, Alexander BD. Prospective aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. *Pediatr Infect Dis J* 2007; 26: 558-564. <https://doi.org/10.1097/INF.0b013e31817197ab> PMID:17596794
36. Hayden R, Pounds S, Knapp K, Petraitiene R, Schaufele RL, Sein T, Walsh TJ. Galactomannan antigenemia in pediatric oncology patients with invasive aspergillosis. *Pediatr Infect Dis J* 2008; 27: 815-819. <https://doi.org/10.1097/INF.0b013e31817197ab> PMID:18703991
37. Castagnola E, Furfaro E, Caviglia I, Licciardello M, Faraci M, Fioredda F, Tomà P, Bandettini R, Machetti M, Viscoli C. 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. <https://doi.org/10.1111/j.1469-0691.2009.03065.x> PMID:20156215
38. Fisher BT, Zaoutis TE, Park JR, Bleakley M, Englund JA, Kane C, Arceci RJ, Guinan E, Smith FO, Luan X, Marr KA. Galactomannan antigen testing for diagnosis of invasive aspergillosis in pediatric hematology patients. *J Pediatric Infect Dis Soc*. 2012; 1: 103-111. <https://doi.org/10.1093/jpids/pis044> PMID:23687575 PMCID:PMC3656552
39. Choi SH, Kang ES, Eo H, Yoo SY, Kim JH, Yoo KH, Sung KW, Koo HH, Kim YJ. Aspergillus galactomannan antigen assay and invasive aspergillosis in pediatric cancer patients and hematopoietic stem cell transplant recipients. *Pediatr Blood Cancer*. 2013; 60: 316-322. <https://doi.org/10.1002/psc.24363> PMID:23042761
40. 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. <https://doi.org/10.1111/myc.12048> PMID:23369047
41. Dinand V, Anjan M, Oberoi JK, Khanna S, Yadav SP, Watal C, Sachdeva A. Threshold of galactomannan antigenemia positivity for early diagnosis of invasive aspergillosis in neutropenic children. *J Microbiol Immunol Infect*. 2016; 49: 66-73. <https://doi.org/10.1016/j.jmii.2013.12.003> PMID:24582464
42. Viscoli C, Machetti M, Cappellano P, B Bucci, P Bruzzi, MT Van Lint, A Bacigalupo. False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004; 38: 913-916. <https://doi.org/10.1086/382224> PMID:14999640
43. Aubry A, Porcher R, Bottero J, Touratier S, Leblanc T, Brethon B, Rousselot P, Raffoux E, Menotti J, Derouin F, Ribaud P, Sulahian A. Occurrence and kinetics of false-positive Aspergillus galactomannan test results following treatment with beta-lactam antibiotics in patients with hematological disorders. *J Clin Microbiol* 2006; 44: 389-394. <https://doi.org/10.1128/JCM.44.2.389-394.2006> PMID:16455889 PMCID:PMC1392647
44. Mennink-Kersten MA, Klont RR, Warris A, Op den Camp HJ, Verweij PE. Bifidobacterium lipoteichoic acid and false ELISA reactivity in Aspergillus antigen detection. *Lancet* 2004; 363: 325-327. [https://doi.org/10.1016/S0140-6736\(03\)15393-7](https://doi.org/10.1016/S0140-6736(03)15393-7)
45. Mennink-Kersten MA, Verweij PE. Non-culture-based diagnostics for opportunistic fungi. *Infect Dis Clin North Am* 2006; 20: 711-727. <https://doi.org/10.1016/j.idc.2006.06.009> PMID:16984877
46. Duarte RF, Sanchez-Ortega I, Cuesta I, Arnan M, Pati-o B, Fernández de Sevilla A, Gudiol C, Ayats J, Cuenca-Estrella M. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis*. 2014; 59: 1696-1702. <https://doi.org/10.1093/cid/ciu673> PMID:25165088
47. Teering S, Verreth A, Peeters A, Van Regenmortel N, De Laet I, Schoonheydt K, Dits H, Van De Vyvere M, Libeer C, Meersseman W, Malbrain ML. Prognostic value of serum galactomannan in mixed icu patients: A retrospective observational study. *Anaesthesiol Intensive Ther*. 2014; 46: 145-154 <https://doi.org/10.5603/AIT.2014.0027> PMID:25078766
48. Challier S, Boyer S, Abachin E, Berche P. Development of a serum-based Taqman real-time PCR assay for diagnosis of invasive aspergillosis. *J Clin Microbiol* 2004; 42: 844-846. <https://doi.org/10.1128/JCM.42.2.844-846.2004> PMID:14766869 PMCID:PMC344496
49. 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. <https://doi.org/10.1080/13693780600939955> PMID:17127630
50. Steinbach WJ, Addison RM, McLaughlin L, Gerrald Q, Martin PL, Driscoll T, Bentsen C, Perfect JR, Alexander BD. Prospective Aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. *Pediatr Infect Dis J* 2007; 26: 558-564. <https://doi.org/10.1097/INF.0b013e31817197ab> PMID:17596794
51. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis* 2006; 42: 1417-1427. <https://doi.org/10.1086/503427> PMID:16619154
52. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: A prospective validation. *Blood*. 2001; 97: 1604-1610. <https://doi.org/10.1182/blood.V97.6.1604> PMID:11238098
53. Hoenigl M, Seeber K, Koidl C, Buzina W, Wölfler A, Duettmann W, Wagner J, Strenger V, Krause R. Sensitivity of galactomannan enzyme immunoassay for diagnosis breakthrough invasive aspergillosis under antifungal prophylaxis and empirical therapy. *Mycoses*. 2013; 56: 471-476. <https://doi.org/10.1111/myc.12060> PMID:23432536
54. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the aspergillus galactomannan enzyme immunoassay. *Clin Infect Dis*. 2005; 40: 1762-1769. <https://doi.org/10.1086/429921> PMID:15909264
55. Cordonnier C, Botterel F, Ben Amor R, Pautas C, Maury S, Kuentz M, Hicheri Y, Bastuji-Garin S, Bretagne S. Correlation between galactomannan antigen levels in serum and neutrophil counts in haematological patients with invasive aspergillosis. *Clin Microbiol Infect*. 2009; 15: 81-86. <https://doi.org/10.1111/j.1469-0691.2008.02122.x> PMID:19154482
56. Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeke E, Wilmer A, Verhaegen J, Boogaerts M, Van Eldere J. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. *Clin Infect Dis*. 2005; 41: 1242-1250. <https://doi.org/10.1086/496927> PMID:16206097
57. Guinea J, Jensen J, Peláez T, Gijón P, Alonso R, Rivera M, Mu-oz P, Bouza E. Value of a single galactomannan determination (platelia) for the diagnosis of invasive aspergillosis in non-hematological patients with clinical isolation of aspergillus spp. *Med Mycol*. 2008; 46: 575-579. <https://doi.org/10.1080/13693780801978968> PMID:19180751
58. Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, Spriet I, Verbeke E, Van Wijngaerden E. Galactomannan in bronchoalveolar lavage fluid: A tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med*. 2008; 177: 27-34. <https://doi.org/10.1164/rccm.200704-606OC> PMID:17885264
59. Husain S, Kwak EJ, Obman A, Wagener MM, Kusne S, Stout JE, McCurry KR, Singh N. Prospective assessment of platelia aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. *Am J Transplant*. 2004; 4: 796-802. <https://doi.org/10.1111/j.1600-6143.2004.00415.x> PMID:15084177
60. Tabarsi P, Soraghi A, Marjani M, Zandian P, Baghaei P, Najafizadeh K, Droudinia A, Sarrafzadeh SA, Javanmard P, Mansouri D. Comparison of serum and bronchoalveolar lavage galactomannan in diagnosing invasive aspergillosis in solid-organ transplant recipients. *Exp Clin Transplant*. 2012; 10: 278-281. <https://doi.org/10.6002/ect.2011.0176> PMID:22631066
61. Guigue N, Menotti J, Ribaud P. False positive galactomannan test after ice-pop ingestion. *N Engl J Med*. 2013; 369: 97-98. <https://doi.org/10.1056/NEJMc1210430> PMID:23822795
62. Petraitiene R, Petraitis V, Witt JR, 3rd, Durkin MM, Bacher JD, Wheat LJ, Walsh TJ. Galactomannan antigenemia after infusion of gluconate-containing plasma-lyte. *J Clin Microbiol*. 2011; 49: 4330-4332. <https://doi.org/10.1128/JCM.05031-11> PMID:21976760 PMCID:PMC3232943
63. Martin-Rabadan P, Gijon P, Alonso Fernandez R, Ballesteros M, Anguita J, Bouza E. False-positive aspergillus antigenemia due to blood product conditioning fluids. *Clin Infect Dis*. 2012; 55: e22-27. <https://doi.org/10.1093/cid/cis493> PMID:22610929
64. Mikulska M, Furfaro E, Del Bono V, Raiola AM, Ratto S, Bacigalupo A, Viscoli C. Piperacillin/tazobactam (tazocintm) seems to be no longer responsible for false-positive results of the galactomannan

- assay. *J Antimicrob Chemother.* 2012; 67: 1746-1748. <https://doi.org/10.1093/jac/dks111> PMID:22499998
65. Vergidis P, Walker RC, Kaul DR, Kauffman CA, Freifeld AG, Slagle DC, Kressel AB, Wheat LJ. False-positive aspergillus galactomannan assay in solid organ transplant recipients with histoplasmosis. *Transpl Infect Dis.* 2012; 14: 213-217. <https://doi.org/10.1111/j.1399-3062.2011.00675.x> PMID:22093368
 66. Huang YT, Hung CC, Liao CH, Sun HY, Chang SC, Chen YC. Detection of circulating galactomannan in serum samples for diagnosis of penicillium marneffeii infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol.* 2007; 45: 2858-2862. <https://doi.org/10.1128/JCM.00050-07> PMID:17596363 PMCid:PMC2045252
 67. Nucci M, Carlesse F, Cappellano P, Varon AG1, Seber A2, Garnica M1, Nouér SA1, Colombo AL. Earlier diagnosis of invasive fusariosis with aspergillus serum galactomannan testing. *PLoS One.* 2014; 9: e87784. <https://doi.org/10.1371/journal.pone.0087784> PMID:24489964 PMCid:PMC3905034
 68. King ST, Stover KR. Considering confounders of the galactomannan index: The role of piperacillin-tazobactam. *Clin Infect Dis.* 2014; 58: 751-752. <https://doi.org/10.1093/cid/cit783> PMID:24280091
 69. Chai LY, Kullberg BJ, Johnson EM, Teerenstra S, Khin LW, Vonk AG, Maertens J, Lortholary O, Donnelly PJ, Schlamm HT, Troke PF, Netea MG, Herbrecht R. Early serum galactomannan trend as a predictor of outcome of invasive aspergillosis. *J Clin Microbiol.* 2012; 50: 2330-2336. <https://doi.org/10.1128/JCM.06513-11> PMID:22553232 PMCid:PMC3405588
 70. Roilides E, Pavlidou E, Papadopoulos F, Panteliadis C, Farmaki E, Tamiolaki M, Sotiriou J. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2003; 18: 450-53. PMID:12736806
 71. Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, Gualandi F, Truini M, and Bacigalupo A. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol* 2002; 40: 1496-1499. <https://doi.org/10.1128/JCM.40.4.1496-1499.2002> PMID:11923380 PMCid:PMC140329
 72. 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. <https://doi.org/10.1128/CVI.00025-07> PMID:17538119 PMCid:PMC1951061
 73. Zhao L, Tang JY, Wang Y, Zhou YF, Chen J, Li BR, Xue HL. [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. PMID:20113658
 74. Mularoni A, Furfaro E, Faraci M, Franceschi A, Mezzano P, Bandettini R, Viscoli C, Castagnola E. High levels of beta-d-glucan in immunocompromised children with proven invasive fungal disease. *Clin Vaccine Immunol.* 2010; 17: 882-883. <https://doi.org/10.1128/CVI.00038-10> PMID:20335432 PMCid:PMC2863371
 75. Badiie P, Alborzi A, Karimi M, Pourabbas B, Haddadi P, Mardaneh J, Moieni M. 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. <https://doi.org/10.3855/jidc.2110> PMID:22505446
 76. Koltze A, Rath P, Schoning S, Steinmann J, Wichelhaus TA, Bader P, Bochennek K, Lehrnbecher T. 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. <https://doi.org/10.1128/JCM.00747-15> PMID:26041896 PMCid:PMC4508457
 77. Ostrosky-Zeichner L, Alexander BD, Kett DH, Vazquez J, Pappas PG, Saeki F, Ketchum PA, Wingard J, Schiff R, Tamura H, Finkelman MA, Rex JH. Multicenter clinical evaluation of the (1->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis* 2005; 41:654-659. <https://doi.org/10.1086/432470> PMID:16080087
 78. Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, Ketchum PA, Finkelman MA, Rex JH, Ostrosky-Zeichner L. Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. *Clin Infect Dis* 2004; 39:199-205 <https://doi.org/10.1086/421944> PMID:15307029
 79. De Pauw B, Walsh TJ, Donnelly JP, David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Mu-oz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett.; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. 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 Grou. *Clin Infect Dis* 2008; 46: 1813-1821 <https://doi.org/10.1086/588660> PMID:18462102 PMCid:PMC2671227
 80. Hummel M, Spiess B, Roder J, von Komorowski G, Dürken M, Kentouche K, Laws HJ, März H, Hehlmann R, Buchheidt D. 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. <https://doi.org/10.1099/jmm.0.007393-0> PMID:19541789
 81. 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. <https://doi.org/10.1007/BF02013825> PMID:8332402
 82. 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. <https://doi.org/10.1097/00006454-200101000-00002> PMID:11176559
 83. Neely M, Margol A, Fu X, van Guilder M, Bayard D, Schumitzky A, Orbach R, Liu S, Louie S, Hope W. Achieving target voriconazole concentrations more accurately in children and adolescents. *Antimicrob Agents Chemother.* 2015; 59: 3090-3097. <https://doi.org/10.1128/AAC.00032-15> PMID:25779580 PMCid:PMC4432122
 84. 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. <https://doi.org/10.1128/AAC.05761-11> PMID:22430956 PMCid:PMC3370730
 85. Gavalda J, Meije Y, Fortun J, Roilides E, Saliba F, Lortholary O, Muñoz P, Grossi P, Cuenca-Estrella M; ESCMID-ECMM-ERS Study Group for Infections in Compromised Hosts. Invasive fungal infections in solid organ transplant recipients. *Clin Microbiol Infect.* 2014; 20 Suppl 7: 27-48. <https://doi.org/10.1111/1469-0691.12660> PMID:24810152
 86. 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. <https://doi.org/10.1111/j.1399-3062.2006.00156.x> PMID:17116134
 87. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, Arikian-Akdagli S, Bassetti M, Bille J, Cornely OA, Cuenca-Estrella M, Donnelly JP, Garbino J, Herbrecht R, Jensen HE, Kullberg BJ, Lass-Flörl C, Lortholary O, Meersseman W, Petrikos G, Richardson MD, Verweij PE, Viscoli C, Ullmann AJ; ESCMID-ECMM-ERS Fungal Infection Study Group. ESCMID-ECMM-ERS* 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: 38-52. <https://doi.org/10.1111/1469-0691.12040> PMID:23137136
 88. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Satoi Y, Lee JM, Walsh TJ; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; 39: 1407-16. 48
 89. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR,

- Gersten ID, Mendizabal AM, Leather HL, Confer DL, Maziarz RT, Stadtmauer EA, Bola-os-Meade J, Brown J, Dipersio JF, Boeckh M, Marr KA; Blood and Marrow Transplant Clinical Trials Network. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010; 116: 5111–5118. <https://doi.org/10.1182/blood-2010-02-268151> PMID:20826719 PMCid:PMC3012532
90. Dvorak CC, Fisher BT, Sung L, Steinbach WJ, Nieder M, Alexander S, Zaoutis TE. Antifungal prophylaxis in pediatric hematology/oncology: new choices and new data. *Pediatr Blood Cancer* 2012; 59: 21–26. <https://doi.org/10.1002/pbc.23415> PMID:22102607 PMCid:PMC4008331
91. Tragiannidis A, Dokos C, Lehrmbecher T, Groll AH. Antifungal chemoprophylaxis in children and adolescents with haematological malignancies and following allogeneic haematopoietic stem cell transplantation: review of the literature and options for clinical practice. *Drugs* 2012; 72: 685–704. <https://doi.org/10.2165/11599810-000000000-00000> PMID:22413762
92. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; 356: 348-359. <https://doi.org/10.1056/NEJMoa061094> PMID:17251531
93. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007; 356: 335-347. <https://doi.org/10.1056/NEJMoa061098> PMID:17251530
94. Ananda-Rajah MR, Grigg A, Downey MT, A Bajel, T Spelman, A Cheng, K T. Thursky, J Vincent, and MA Slavin. 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. <https://doi.org/10.3324/haematol.2011.051995> PMID:22058198 PMCid:PMC3291603
95. Ananda-Rajah MR, Grigg A, Slavin MA. Making sense of posaconazole therapeutic drug monitoring: A practical approach. *Curr Opin Infect Dis*. 2012; 25: 605-611. <https://doi.org/10.1097/QCO.0b013e328359a56e> PMID:23086185
96. Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clin Pharmacol Ther*. 2011; 89: 351-352. <https://doi.org/10.1038/clpt.2010.261> PMID:21270787
97. 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. <https://doi.org/10.1592/phco.27.12.1627> PMID:18041883
98. Welzen ME, Bruggemann RJ, Van Den Berg JM, Voogt HW, Gilissen JH, Pajkrt D, Klein N, Burger DM, Warris A. A twice daily posaconazole dosing algorithm for children with chronic granulomatous disease. *Pediatr Infect Dis J*. 2011; 30: 794-797. <https://doi.org/10.1097/INF.0b013e3182195808> PMID:21772229
99. Doring M, Muller C, Johann PD, Erbacher A, Kimmig A, Schwarze CP, Lang P, Handgretinger R, Müller I. 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. <https://doi.org/10.1186/1471-2334-12-263> PMID:23082876 PMCid:PMC3514296
100. Lehrmbecher T, Attarbaschi A, Duerken M, Garbino J, Gruhn B, Kontny U, Lüer S, Phillips R, Scholz J, Wagner HJ, Wiesel T, Groll AH. Posaconazole salvage treatment in paediatric patients: A multicentre survey. *Eur J Clin Microbiol Infect Dis*. 2010; 29: 1043-1045. <https://doi.org/10.1007/s10096-010-0957-4> PMID:20495990
101. Marks DI, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, Miller PJ, Ribaud P, Schlam HT, Solano C, Cook G; IMPROVIT Study Group. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol*. 2011; 155: 318-327. <https://doi.org/10.1111/j.1365-2141.2011.08838.x> PMID:21880032 PMCid:PMC3253339
102. Mattiuzzi GN, Cortes J, Alvarado G, Verstovsek S, Koller C, Pierce S, Blamble D, Faderl S, Xiao L, Hernandez M, Kantarjian H. 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. <https://doi.org/10.1007/s00520-009-0783-3> PMID:19956980
103. Barreto JN, Beach CL, Wolf RC, Merten JA, Tosh PK, Wilson JW, Hogan WJ, Litzow MR. 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. <https://doi.org/10.1002/ajh.23388> PMID:23460251
104. Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, Adamson P, Saez-Llorens X, Vora AJ, Arrieta AC, Blumer J, Lutsar I, Milligan P, Wood N. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother*. 2004; 48: 2166-2172. <https://doi.org/10.1128/AAC.48.6.2166-2172.2004> PMID:15155217 PMCid:PMC415618
105. Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother*. 2009; 53: 935-944. <https://doi.org/10.1128/AAC.00751-08> PMID:19075073 PMCid:PMC2650527
106. Driscoll TA, Frangoul H, Nemecek ER, Murphey DK, Yu LC, Blumer J, Krance RA, Baruch A, Liu P. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. *Antimicrob Agents Chemother*. 2011; 55: 5780-5789. <https://doi.org/10.1128/AAC.05010-11> PMID:21911570 PMCid:PMC3232803
107. Soler-Palacin P, Frick MA, Martin-Nalda A, Lanaspá M, Pou L, Roselló E, de Heredia CD, Figueras C. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: A prospective study. *J Antimicrob Chemother*. 2012; 67: 700-706. <https://doi.org/10.1093/jac/dkr517> PMID:22190607
108. 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. <https://doi.org/10.1093/jac/dks258> PMID:22796890
109. Molina JR, Serrano J, Sanchez-Garcia J, Rodríguez-Villa A, Gómez P, Tallón D, Martín V, Rodríguez G, Rojas R, Martín C, Martínez F, Alvarez MA, Torres A. Voriconazole as primary antifungal prophylaxis in children undergoing allo-sct. *Bone Marrow Transplant*. 2012; 47: 562-567. <https://doi.org/10.1038/bmt.2011.111> PMID:21572466
110. 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. <https://doi.org/10.1128/AAC.01083-10> PMID:21768513 PMCid:PMC3186950
111. Park WB, Kim N-H, Kim K-H, Lee SH, Nam WS, Yoon SH, Song KH, Choe PG, Kim NJ, Jang IJ, Oh MD, Yu KS. 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. <https://doi.org/10.1093/cid/cis599> PMID:22761409
112. Winston DJ, Maziarz RT, Chandrasekar PH, Lazarus HM, Goldman M, Blumer JL, Leitz GJ, Territo MC. 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. *Ann Intern Med*. 2003; 138: 705-713. <https://doi.org/10.7326/0003-4819-138-9-200305060-00006> PMID:12729424
113. Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, Balajee SA, Nichols WG, Musher B, Corey L. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004; 103: 1527-1533. <https://doi.org/10.1182/blood-2003-08-2644> PMID:14525770
114. Marr KA, Leisenring W, Crippa F, Slattery JT, Corey L, Boeckh M, McDonald GB. Cyclophosphamide metabolism is affected by azole antifungals. *Blood*. 2004; 103: 1557-1559.

- <https://doi.org/10.1182/blood-2003-07-2512> PMID:14504090
115. Menichetti F, Del Favero A, Martino P, Bucaneve G, Micozzi A, Girmenia C, Barbabietola G, Pagaño L, Leoni P, Specchia G, Caiozzo A, Raimondi R, Mandelli F. 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. <https://doi.org/10.1086/515129> PMID:10064240
 116. Prentice HG, Caillot D, Dupont B, Menichetti F, Schuler U. Oral and intravenous itraconazole for systemic fungal infections in neutropenic haematological patients: Meeting report. London, united kingdom, 20 june 1998. Acta Haematol. 1999; 101: 56-62. <https://doi.org/10.1159/000040923> PMID:10085441
 117. Harousseau JL, Dekker AW, Stamatoullas-Bastard A, Fassas A, Linkesch W, Gouveia J, De Bock R, Rovira M, Seifert WF, Joosen H, Peeters M, De Beule K. 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. <https://doi.org/10.1128/AAC.44.7.1887-1893.2000> PMID:10858349 PMID:C10858349
 118. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, Eisenstein EM, Turner ML, DeCarlo ES, Starling JM, Holland SM. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med. 2003; 348: 2416-2422. <https://doi.org/10.1056/NEJMoa021931> PMID:12802027
 119. de Repentigny L, Ratelle J, Leclerc JM, Cornu G, Sokal EM, Jacqmin P, De Beule K. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. Antimicrob Agents Chemother. 1998; 42: 404-408. PMID:9527794 PMID:C105422
 120. Groll AH, Wood L, Roden M, Mickiene D, Chiou CC, Townley E, Dad L, Piscitelli SC, Walsh TJ. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. Antimicrob Agents Chemother. 2002; 46: 2554-2563. <https://doi.org/10.1128/AAC.46.8.2554-2563.2002> PMID:12121932 PMID:C12121932
 121. 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. <https://doi.org/10.1038/sj.bmt.1702023> PMID:10578159
 122. Simon A, Besuden M, Vezmar S, Hasan C, Lampe D, Kreutzberg S, Glasmacher A, Bode U, Fleischhack G. Itraconazole prophylaxis in pediatric cancer patients receiving conventional chemotherapy or autologous stem cell transplants. Support Care Cancer. 2007; 15: 213-220. <https://doi.org/10.1007/s00520-006-0125-7> PMID:16944217
 123. 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-β-cyclodextrin oral solution or coated-pellet capsules. Mycoses. 1999; 42: 591-600. <https://doi.org/10.1046/j.1439-0507.1999.00518.x> PMID:10680434
 124. Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Sparrelid E, Tydén G. Prophylactic use of liposomal amphotericin b (ambisome) against fungal infections: A randomized trial in bone marrow transplant recipients. Transplant Proc. 1993; 25: 1495-1497. PMID:8442163
 125. 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. PMID:8136741
 126. Kelsey SM, Goldman JM, McCann S, Newland AC, Scarffe JH, Oppenheim BA, Mufti GJ. 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. <https://doi.org/10.1038/sj.bmt.1701543> PMID:10197802
 127. Penack O, Schwartz S, Martus P, Reinwald M, Schmidt-Hieber M, Thiel E, Blau IW. 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. <https://doi.org/10.1093/annonc/mdl128> PMID:16766594
 128. Hong Y, Shaw PJ, Nath CE, Yadav SP, Stephen KR, Earl JW, McLachlan AJ. Population pharmacokinetics of liposomal amphotericin b in pediatric patients with malignant diseases. Antimicrob Agents Chemother. 2006; 50: 935-942. <https://doi.org/10.1128/AAC.50.3.935-942.2006> PMID:16495254 PMID:C1426421
 129. Ringden O, Meunier F, Tollemar J, Ricci P, Tura S, Kuse E, Viviani MA, Gorin NC, Klastersky J, Fenaux P. 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.
 130. 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. <https://doi.org/10.1093/jac/dkp196> PMID:19491205
 131. Huang X, Chen H, Han M, Zou P, Wu D, Lai Y, Huang H, Chen X, Liu T, Zhu H, Wang J, Hu J. 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 Transplant. 2012; 18: 1509-1516. <https://doi.org/10.1016/j.bbmt.2012.03.014> PMID:22469884
 132. Seibel NL, Schwartz C, Arrieta A, Flynn P, Shad A, Albano E, Keirns J, Lau WM, Facklam DP, Buell DN, Walsh TJ. Safety, tolerability, and pharmacokinetics of micafungin (fk463) in febrile neutropenic pediatric patients. Antimicrob Agents Chemother. 2005; 49: 3317-3324. <https://doi.org/10.1128/AAC.49.8.3317-3324.2005> PMID:16048942 PMID:C1196271
 133. Hope WW, Seibel NL, Schwartz CL, Arrieta A, Flynn P, Shad A, Albano E, Keirns JJ, Buell DN, Gumbo T, Drusano GL, Walsh TJ. Population pharmacokinetics of micafungin in pediatric patients and implications for antifungal dosing. Antimicrob Agents Chemother. 2007; 51: 3714-3719. <https://doi.org/10.1128/AAC.00398-07> PMID:17638696 PMID:C1043253
 134. Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. Pediatr Infect Dis J. 2011; 30: e97-e102. <https://doi.org/10.1097/INF.0b013e3182127eaf> PMID:21378595
 135. Mehta PA, Vinks AA, Filipovich A, Bleesing J, Jodele S, Jordan MB, Marsh R, Tarin R, Edwards S, Fearing D, Lawrence J, Davies SM. Alternate-day micafungin antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: A pharmacokinetic study. Biol Blood Marrow Transplant. 2010; 16: 1458-1462. <https://doi.org/10.1016/j.bbmt.2010.05.002> PMID:20546908
 136. Beaute J, Obenga G, Le Mignot L, Mahlaoui N, Bougnoux ME, Mouy R, Gougerot-Pocidal MA, Barlogis V, Suarez F, Lantermier F, Hermine O, Lecuit M, Blanche S, Fischer A, Lortholary O; French PID Study Group CEREDIH. 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. <https://doi.org/10.1097/INF.0b013e3181f13b23> PMID:20700078
 137. Mouy R, Veber F, Blanche S, Donadieu J, Brauner R, Levron JC, Griscelli C, Fischer A. Long-term itraconazole prophylaxis against aspergillus infections in thirty-two patients with chronic granulomatous disease. J Pediatr. 1994; 125: 998-1003. [https://doi.org/10.1016/S0022-3476\(05\)82023-2](https://doi.org/10.1016/S0022-3476(05)82023-2)
 138. Lester JM, Smith PB, Cohen-Wolkowicz M, Benjamin DK Jr, Hope WW. Antifungal agents and therapy for infants and children with invasive fungal infections: a pharmacological perspective. Br J Clin Pharmacol 2013; 75: 1381-95. 5
 139. Herbrecht R, Flückiger U, Gachot B, Ribaud P, Tiebaut A, Cordonnier C. Treatment of invasive candida and invasive aspergillus infections in adult haematological patients. Eur J Cancer 2007; 5:49-59. <https://doi.org/10.1016/j.ejcsup.2007.06.007>
 140. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frère P, Gachot B, Heinz WJ, Lass-Flörl C, Ribaud P, Thiebaut A, Cordonnier C; Third European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. Bone Marrow Transplant 2011; 46: 709-18. <https://doi.org/10.1038/bmt.2010.175> PMID:20661235
 141. Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections:

- evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther* 2010; 88: 115–119. <https://doi.org/10.1038/clpt.2010.64> PMID:20505665
142. Groll AH, Tragiannidis A. Update on antifungal agents for paediatric patients. *Clin Microbiol Infect* 2010; 16: 1343–53. <https://doi.org/10.1111/j.1469-0691.2010.03334.x> PMID:20678177
 143. Sung L, Phillips R, Lehrnbecher T. Time for paediatric febrile neutropenia guidelines—children are not little adults. *Eur J Cancer* 2011; 47: 811–813. <https://doi.org/10.1016/j.ejca.2011.01.021> PMID:21371884
 144. Allinson K, Kolve H, Gumbinger HG, Vormoor HJ, Ehler K, Groll AH. Secondary antifungal prophylaxis in paediatric allogeneic haematopoietic stem cell recipients. *J Antimicrob Chemother* 2008; 61: 734–742. <https://doi.org/10.1093/jac/dkm521> PMID:18238891
 145. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, Pigneux A, Cornely OA, Ullmann AJ, Bofarull RM, de la Cámara R, Weisser M, Liakopoulou E, Abecasis M, Heussel CP, Pineau M, Ljungman P, Einsele H; Voriconazole for Secondary Prophylaxis of Invasive Fungal Infections in Patients With Allogeneic Stem Cell Transplants (VOSIFI) study group; Infectious Diseases Working Party, European Group for Blood and Marrow Transplantation. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica* 2010; 95: 1762–1768. <https://doi.org/10.3324/haematol.2009.020073> PMID:20634495 PMCid:PMC2948103
 146. McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, Warnock DW. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis*. 2001; 33: 641–647. <https://doi.org/10.1086/322606> PMID:11486286
 147. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis*. 1999; 29: 239–244. <https://doi.org/10.1086/520192> PMID:10476719
 148. Sung L, Lange BJ, Gerbing RB, Alonzo TA, Feusner J. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. *Blood*. 2007; 110:3532–3539. <https://doi.org/10.1182/blood-2007-05-091942> PMID:17660380
 149. Walsh TJ, Driscoll T, Milligan PA, Wood ND, Schlamm H, Groll AH, Jafri H, Arrieta AC, Klein NJ, Lutsar I. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother* 2010; 54:4116–4123. <https://doi.org/10.1128/AAC.00896-10> PMID:20660687 PMCid:PMC2944563
 150. Walsh TJ, Adamson PC, Seibel NL, Flynn PM, Neely MN, Schwartz C, Shad A, Kaplan SL, Roden MM, Stone JA, Miller A, Bradshaw SK, Li SX, Sable CA, Kartsonis NA. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother* 2005; 49:4536–4545. <https://doi.org/10.1128/AAC.49.11.4536-4545.2005> PMID:16251293 PMCid:PMC1280172
 151. Benjamin DKJ, Driscoll T, Seibel NL, Gonzalez CE, Roden MM, Kilaru R, Clark K, Dowell JA, Schranz J, Walsh TJ. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; 50:632–638. <https://doi.org/10.1128/AAC.50.2.632-638.2006> PMID:16436720 PMCid:PMC1366891
 152. Caillot D, Thiébaud A, Herbrecht R, de Botton S, Pigneux A, Bernard F, Larché J, Monchecourt F, Alfandari S, Mahi L. 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. <https://doi.org/10.1002/cncr.23109> PMID:17941026
 153. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis* 2004; 39: 797–802. <https://doi.org/10.1086/423380> PMID:15472810
 154. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, Haas A, Ruhnke M, Lode H. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis*. 2002; 34: 563–571. <https://doi.org/10.1086/324620> PMID:11807679
 155. Fortun J, Martín-Davila P, Sanchez MA, Pintado V, Alvarez ME, Sánchez-Sousa A, Moreno S. Voriconazole in the treatment of invasive mold infections in transplant recipients. *Eur J Clin Microbiol Infect Dis*. 2003; 22: 408–413. <https://doi.org/10.1007/s10096-003-0960-0> PMID:12827536
 156. 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. <https://doi.org/10.1016/j.healun.2003.10.014> PMID:15653389
 157. Veroux M, Corona D, Gagliano M, Sorbello M, Macarone M, Cutuli M, Giuffrida G, Morello G, Paratore A, Veroux P. Voriconazole in the treatment of invasive aspergillosis in kidney transplant recipients. *Transplant Proc*. 2007; 39: 1838–1840. <https://doi.org/10.1016/j.transproceed.2007.05.012> PMID:17692627
 158. Doby EH, Benjamin DK, Jr., Blaschke AJ, Ward RM, Pavia AT, Martin PL, Driscoll TA, Cohen-Wolkowicz M, Moran C. 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. <https://doi.org/10.1097/INF.0b013e31824acc33> PMID:22301479 PMCid:PMC3356483
 159. Bartelink IH, Wolfs T, Jonker M, de Waal M, Egberts TC, Ververs TT, Boelens JJ, Bierings M. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. *Antimicrob Agents Chemother*. 2013; 57: 235–240. <https://doi.org/10.1128/AAC.01540-12> PMID:23114771 PMCid:PMC3535953
 160. 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. [https://doi.org/10.1016/S0378-5173\(02\)00066-2](https://doi.org/10.1016/S0378-5173(02)00066-2)
 161. Bochenek 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. <https://doi.org/10.1111/j.1469-0691.2011.03483.x> PMID:21895857
 162. Groll AH, Silling G, Young C, Schwerdtfeger R, Ostermann H, Heinz WJ, Gerss J, Kolve H, Lanvers-Kaminsky C, Vieira Pinheiro JP, Gammelin S, Cornely OA, Wuerthwein G. 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. <https://doi.org/10.1128/AAC.00425-10> PMID:20660670 PMCid:PMC2944616
 163. K, Tsukimoto I, Tsunematsu Y, Honda M, Iwai N, Maniwa T, Haigo H, Suzuki K, Mori T. Evaluation of the safety and efficacy of liposomal amphotericin b (l-amb) in children. *J Infect Chemother*. 2012; 18: 456–465. <https://doi.org/10.1007/s10156-011-0357-4> PMID:22286407
 164. Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R, Schwartz S, Ullmann AJ, Meert L, Paesmans M, Marchetti O, Akan H, Ameye L, Shivaprakash M, Viscoli C. 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. <https://doi.org/10.1038/bmt.2009.334> PMID:20062093
 165. Viscoli C, Herbrecht R, Akan H, Baila L, Sonet A, Gallamini A, Giagounidis A, Marchetti O, Martino R, Meert L, Paesmans M, Ameye L, Shivaprakash M, Ullmann AJ, Maertens J; Infectious Disease Group of the EORTC. An eortc phase ii study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. *J Antimicrob Chemother*. 2009; 64: 1274–1281. <https://doi.org/10.1093/jac/dkp355> PMID:19841031
 166. Cornely OA, Vehreschild JJ, Vehreschild MJ, Würthwein G, Arenz D, Schwartz S, Heussel CP, Silling G, Mahne M, Franklin J, Harnischmacher U, Wilkens A, Farowski F, Karthaus M, Lehrnbecher T, Ullmann AJ, Hallek M, Groll AH. Phase ii dose escalation study of caspofungin for invasive aspergillosis. *Antimicrob Agents Chemother*. 2011; 55: 5798–5803. <https://doi.org/10.1128/AAC.05134-11> PMID:21911573 PMCid:PMC3232774
 167. Groetzner J, Kaczmarek I, Wittwer T, Strauch J, Meiser B, Wahlers T, Daebritz S, Reichart B. Caspofungin as first-line therapy for the treatment of invasive aspergillosis after thoracic organ transplantation. *J Heart Lung Transplant*. 2008; 27: 1–6. <https://doi.org/10.1016/j.healun.2007.10.002> PMID:18187079
 168. Winkler M, Pratschke J, Schulz U, Zheng S, Zhang M, Li W, Lu M, Sgarabotto D, Sganga G, Kaskel P, Chandwani S, Ma L, Petrovic J,

- Shivaprakash M. Caspofungin for post solid organ transplant invasive fungal disease: Results of a retrospective observational study. *Transpl Infect Dis.* 2010; 12: 230-237. <https://doi.org/10.1111/j.1399-3062.2009.00490.x> PMID:20070619 PMCid:PMC2904899
169. Neely M, Jafri HS, Seibel N, Knapp K, Adamson PC, Bradshaw SK, Strohmaier KM, Sun P, Bi S, Dockendorf MF, Stone JA, Kartsonis NA. Pharmacokinetics and safety of caspofungin in older infants and toddlers. *Antimicrob Agents Chemother.* 2009; 53: 1450-1456. <https://doi.org/10.1128/AAC.01027-08> PMID:19114680 PMCid:PMC2663098
170. Cesaro S, Giacchino M, Locatelli F, Spiller M, Buldini B, Castellini C, Caselli D, Giraldo E, Tucci F, Tridello G, Rossi MR, Castagnola E. 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. <https://doi.org/10.1186/1471-2334-7-28> PMID:17442100 PMCid:PMC1871594
171. Zaoutis T, Lehrmbecher T, Groll AH, Steinbach WJ, Jafri HS, Maertens J, Ngai AL, Chow JW, Taylor AF, Strohmaier KM, Bourque M, Bradshaw SK, Petrecz M, Kartsonis NA. Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J.* 2009; 28: 1132-1135. <https://doi.org/10.1097/INF.0b013e3181af5a15> PMID:19779392
172. Zaoutis TE, Jafri HS, Huang LM, Locatelli F, Barzilay A, Ebell W, Steinbach WJ, Bradley J, Lieberman JM, Hsiao CC, Seibel N, Laws HJ, Gamba M, Petrecz M, Taylor AF, Strohmaier KM, Chow JW, Kartsonis NA, Ngai AL. A prospective, multicenter study of caspofungin for the treatment of documented candida or aspergillus infections in pediatric patients. *Pediatrics.* 2009; 123: 877-884. <https://doi.org/10.1542/peds.2008-1158> PMID:19255017
173. 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. <https://doi.org/10.1016/j.ijantimicag.2011.07.008> PMID:21925846
174. Marr KAS, Rottinghaus H, Jagannatha S, H Jagannatha, E J. Bow, JR. Wingard, P Pappas, RHerbrecht, TJ. Walsh, J Maertens and the Mycoses Study Group. A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis. 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); London, UK; March 31–April 3, 2012. Abstract LB2812.
175. Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Ellis D, Tullio V, Rodloff A, Fu W, Ling TA; Global Antifungal Surveillance Group. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. *J Clin Microbiol* 2010; 48: 1366–1377. <https://doi.org/10.1128/JCM.02117-09> PMID:20164282 PMCid:PMC2849609
176. Maertens J, Glasmacher A, Herbrecht R, Thiebaut A, Cordonnier C, Segal BH, Killar J, Taylor A, Kartsonis N, Patterson TF, Aoun M, Caillot D, Sable C; 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. <https://doi.org/10.1002/cncr.22348> PMID:17103444
177. Glasmacher A, Hahn C, Leutner C, Molitor E, Wardelmann E, Losem C, Sauerbruch T, Marklein G, Schmidt-Wolf IG. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses.* 1999; 42: 443-451. <https://doi.org/10.1046/j.1439-0507.1999.00505.x> PMID:10546485
178. Trifilio S, Singhal S, Williams S, Frankfurt O, Gordon L, Evens A, Winter J, Tallman M, Pi J, Mehta J. Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant.* 2007; 40: 451-456. <https://doi.org/10.1038/sj.bmt.1705754> PMID:17589527
179. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, Greene RE, Hachem R, Hadley S, Herbrecht R, Langston A, Louie A, Ribaud P, Segal BH, Stevens DA, van Burik JA, White CS, Corcoran G, Gogate J, Krishna G, Pedicone L, Hardalo C, Perfect JR. 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. <https://doi.org/10.1086/508774> PMID:17143808
180. Denning DW, Marr KA, Lau WM, Facklam DP, Ratanatharathorn V, Becker C, Ullmann AJ, Seibel NL, Flynn PM, van Burik JA, Buell DN, Patterson TF. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect* 2006; 53:337–349. <https://doi.org/10.1016/j.jinf.2006.03.003> PMID:16678903
181. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis. *N Engl J Med.* 2002; 347: 408-415. <https://doi.org/10.1056/NEJMoa020191> PMID:12167683
182. Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, Hodges M, Groll AH, Perfect JR. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J.* 2002; 21: 240-248. <https://doi.org/10.1097/00006454-200203000-00015> PMID:12005089
183. Maertens J, Raad I, Petrikos G, Boogaerts M, Selleslag D, Petersen FB, Sable CA, Kartsonis NA, Ngai A, Taylor A, Patterson TF, Denning DW, Walsh TJ; 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. <https://doi.org/10.1086/423381> PMID:15578352
184. Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, Heussel CP, Lortholary O, Rieger C, Boehme A, Aoun M, Horst HA, Thiebaut A, Ruhnke M, Reichert D, Vianelli N, Krause SW, Olavarria E, Herbrecht R; AmBioLoad Trial Study Group. Liposomal amphotericin b as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (ambiloal trial). *Clin Infect Dis.* 2007; 44: 1289-1297. <https://doi.org/10.1086/514341> PMID:17443465
185. Raad, II, Hanna HA, Boktour M, Jiang Y, Torres HA, Afif C, Kontoyiannis DP, Hachem RY. Novel antifungal agents as salvage therapy for invasive aspergillosis in patients with hematologic malignancies: Posaconazole compared with high-dose lipid formulations of amphotericin b alone or in combination with caspofungin. *Leukemia.* 2008; 22: 496-503. <https://doi.org/10.1038/sj.leu.2405065> PMID:18094720
186. 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. <https://doi.org/10.1093/jac/dkp397> PMID:19887460
187. 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. <https://doi.org/10.1016/j.bbmt.2010.04.017> PMID:20460163
188. De la Serna J, Jarque I, Lopez-Jimenez J, Vallejo C. 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. PMID:23546466
189. 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. <https://doi.org/10.1093/jac/dks189> PMID:22653819
190. Maertens J, Raad I, Petrikos G, Boogaerts M, Selleslag D, Petersen FB, Sable CA, Kartsonis NA, Ngai A, Taylor A, Patterson TF, Denning DW, Walsh TJ; 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. <https://doi.org/10.1086/423381> PMID:15578352
191. Perfect JR, Marr KA, Walsh TJ, Greenberg RN, DuPont B, de la Torre-Cisneros J, Just-Nübling G, Schlamm HT, Lutsar I, Espinel-

- Ingroff A, Johnson E. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; 36:1122–31. <https://doi.org/10.1086/374557> PMID:12715306
192. Ng TT, Denning DW. Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections. Evaluation of United Kingdom compassionate use data. *Arch Intern Med* 1995; 155:1093–1098. <https://doi.org/10.1001/archinte.1995.00430100129015>
193. Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, Silber JL, DiNubile MJ, Reboli A, Bow E, Lister J, Anaissie EJ. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998; 26:1383–1396. <https://doi.org/10.1086/516353> PMID:9636868
194. Prentice HG, Hann IM, Herbrecht R, Aoun M, Kvaloy S, Catovsky D, Pinkerton CR, Schey SA, Jacobs F, Oakhill A, Stevens RF, Darbyshire PJ, Gibson BE. 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. <https://doi.org/10.1046/j.1365-2141.1997.2473063.x> PMID:9332329
195. Maertens JA, Madero L, Reilly AF, Lehrnbecher T, Groll AH, Jafri HS, Green M, Nania JJ, Bourque MR, Wise BA, Strohmaier KM, Taylor AF, Kartsonis NA, Chow JW, Arndt CA, DePauw BE, Walsh TJ; Caspofungin Pediatric Study Group. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin b for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J*. 2010; 29: 415-420. <https://doi.org/10.1097/INF.0b013e3181da2171> PMID:20431381
196. Caselli D, Paolicchi O. Empiric antibiotic therapy in a child with cancer and suspected septicemia. *Pediatr Rep*. 2012; 4: e2. <https://doi.org/10.4081/pr.2012.e2> PMID:22690308 PMCID:PMC3357615
197. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, Dhédin N, Isnard F, Ades L, Kuhnowski F, Foulet F, Kuentz M, Maison P, Bretagne S, Schwarzinger M. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. *Clin Infect Dis*. 2009; 48: 1042-1051. <https://doi.org/10.1086/597395> PMID:19281327
198. Girmenia C, Micozzi A, Gentile G, Santilli S, Arleo E, Cardarelli L, Capria S, Minotti C, Cartoni C, Brocchieri S, Guerrisi V, Meloni G, Foà R, Martino P. Clinically driven diagnostic antifungal approach in neutropenic patients: A prospective feasibility study. *J Clin Oncol*. 2010; 28: 667-674. <https://doi.org/10.1200/JCO.2009.21.8032> PMID:19841328
199. Tan BH, Low JG, Chlebicka NL, Kurup A, Cheah FK, Lin RT, Goh YT, Wong GC. Galactomannan-guided preemptive vs. Empirical antifungals in the persistently febrile neutropenic patient: A prospective randomized study. *Int J Infect Dis*. 2011; 15: e350-356. <https://doi.org/10.1016/j.ijid.2011.01.011> PMID:21397541
200. Castagnola E, Bagnasco F, Amoroso L, Caviglia I, Caruso S, Faraci M, Calvillo M, Moroni C, Bandettini R, Cangemi G, Magnano GM, Buffa P, Moscatelli A, Haupt R. 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. <https://doi.org/10.1097/INF.000000000000101> PMID:24136371
201. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 52: 427–431. <https://doi.org/10.1093/cid/ciq147> PMID:21205990