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Review Article

Invasive Aspergillosis in Children: Update on Current Guidelines

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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.

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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 *ß*-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 *ß*-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 ≥ 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>2years Allo-HSCT with or without GVHD No grading De-novo or recurrent leukaemias	A-IIt for children>2years 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-IIt 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-IIt 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>13years Allogeneic HSCT without GVHD B-I for children>13years Allogenic HSCT with GVHD B-I for children>13years De-novo or recurrent leukaemias	A-IIt for children>13years 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>13years 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-IIt 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-IIt 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 Aspergillus 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, CVHD, 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 granulocytopaenic 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.

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