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Antifungal management in adults and children with hematological malignancies or undergoing hematopoietic cell transplantation: recommendations of Polish Society of Hematology and Blood Transfusion, Polish Society of Pediatric Oncology and Hematology, and Polish Adult Leukemia Study Group, 2020

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Abstract

Invasive fungal disease (IFD) is one of the most serious complications of therapy in patients with immune suppression. It particularly concerns patients treated for malignant hematological diseases, immune deficiencies, or undergoing hematopoietic cell transplantation (HCT). Development of IFD can abrogate the effect of previous therapy and contributes to dismal outcome of the underlying disease. The Working Group consisting of members of the Polish Society of Hematology and Blood Transfusion, the Polish Society of Pediatric Oncology and Hematology, and the Polish Adult Leukemia Study Group has prepared recommendations for the diagnostic and therapeutic management of IFD in adults and children. This paper presents the current recommendations for patients in immune suppression treated in Polish pediatric and adult hematology and HCT centers, based on the guidelines of the European Conference on Infections in Leukaemia (ECIL) 2015–2019. Levels of diagnosis of IFD (possible, probable, and proven) and antifungal management (prophylaxis, as well as empirical and targeted therapies) are declared according to updated international criteria of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) 2019. Patients with primary diagnosis of acute lymphoblastic leukemia, acute myeloblastic leukemia, severe aplastic anemia, chronic granulomatous disease, and severe combined immunodeficiency, as well as patients after allogeneic HCT, are included in the high-risk groups for development of IFD. For these patients, antifungal prophylaxis based on azoles or micafungin is recommended. In empirical therapy, caspofungin or liposomal/lipid formulas of amphotericin B are recommended. The Working Group has discouraged the use of itraconazole in capsules and amphotericin deoxycholate. Detailed guidelines for first- and second-line targeted therapies for invasive candidiasis, aspergillosis, mucormycosis, fusariosis, and scedosporiosis, as well as the principles of the recommended dosing of antifungals, are presented in this paper.

Keywords:
invasive fungal infections, invasive fungal disease, diagnostics, prophylaxis, therapy, children

Introduction

Invasive fungal disease (IFD) is one of the most serious complications during and after hematopoietic stem cell transplantation (HCT), in anticancer therapy – especially in hematology, as well as in patients with other severe immune suppression states, such as severe aplastic anemia (SAA) or primary immunodeficiency diseases (PIDs) [1].

The epidemiology of IFD has evolved considerably over the past decades, in association with advances in supportive care, in particular, in prophylaxis and therapy of IFD. Retrospective analyses and prospective studies indicate that patients at the highest risk for the development of IFD are those undergoing intensive chemotherapy for acute myeloid leukemia (AML) and those treated with allogeneic hematopoietic stem cell transplantation (allo-HCT) [2, 3]. Recent data, however, confirm an equally high risk of IFD among selected patients with lymphomas and acute lymphoblastic leukemia (ALL).

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The current incidence of IFD in Poland is 21.2% in children after HCT, 8.8% in children undergoing anticancer treatment [4, 5, 6], and 6.3% in adults after HCT [3]. However, the incidence of IFD is even higher in some subpopulations: 28.3% and 14.0%, respectively, in children and adults undergoing allo-HCT; 29.4% and 11.3%, respectively, in children and adults with ALL; and 41.2% and 13.2%, respectively, in children and adults with AML [3]. Introduction of the national program of antifungal prophylaxis with reimbursement of posaconazole and voriconazole in selected high-risk groups of patients in 2014–2015 has resulted in a decrease of IFD incidence, confirmed in pediatric patients [4].

The most common IFD in patients treated intensively is invasive aspergillosis (IA), usually caused by *Aspergillus fumigatus*. A large retrospective Italian analysis, covering >11,000 patients treated with hematologic malignancies, showed an occurrence of IA at the level of 2.6%, but among AML patients, this percentage was as high as 12% [7]. In allo-HCT recipients, IA is diagnosed with a frequency of 5.8%–10% depending on the type of transplantation and the intensity of the immunosuppressive procedure. In >90% of IA cases, pulmonary disease is found [invasive pulmonary aspergillosis (IPA)], but aspergillosis with involvement of the paranasal sinuses and the central nervous system (CNS) is also observed, as are the disseminated forms. IA-related mortality in patients treated conventionally and after allo-HCT reaches 27% and 40%, respectively, and is lower than in the previous decade [7].

An important problem noted in recent years is the increase in the incidence of IFD caused by mold fungi other than *Aspergillus*, in particular, *Mucorales*, *Fusarium* spp., and *Scedosporium* spp. Mucormycosis currently accounts for about 7% of invasive fungal infections, is characterized by high mortality (>60%), and often coexists with aspergillosis [2, 8, 9]. Mucormycosis is more common among the elderly and in patients with concomitant diseases, such as diabetes, renal failure, and malnutrition, and is usually difficult to diagnose. In its clinical course, involvement of the CNS, nasal sinuses, and lungs is observed, and disseminated forms are also observed.

Over the past 20 years, a significant improvement in the diagnostics and classification of IFD [1], in addition to development of antifungal drugs, has been achieved. Nevertheless, IFD remains one of the most frequent infections in these patient populations. The joint group of members of Polish hematology scientific societies aims to provide clinicians with best guidance in their everyday working practice. The objective of this paper is to provide comprehensive Polish guidelines focusing on the life-threatening IFDs.

Methods

The Working Group was created by members of the Polish Society of Hematology and Blood Transfusion, the Polish Society of Pediatric Oncology and Hematology, and the Polish Adult Leukemia Study Group with the task to prepare guidelines for the management of patients treated in the departments of hematology, HCT, and pediatric hematology and oncology. Recommendations for adults treated in hematology and/or HCT centers, as well as for children treated in oncology/hematology and/or HCT centers, were prepared based on previous Polish guidelines [10], current recommendations from the ECIL [11, 12, 13], the Infectious Diseases Society of America (IDSA) [14–17], and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [18], supplemented by ECIL-8 guidelines (www.ecil-leukaemia.com) and literature from the past 5 years. Specificity of the Polish health-care system was taken into account. The recommendations were graded according to the modified ECIL-8 grading system (Tab. I).

Risk groups

Based on international guidelines [13], previous Polish pediatric guidelines [10], current epidemiological Polish data [3, 4], and clinical experience, the Working Group stratified patients into various risk groups. The high-risk group for development of IFD includes the following diagnoses: ALL, AML, myelodysplastic syndromes (MDSs), SAA, chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID), as well as patients after allo-HCT. All other patients are regarded as being in the low-risk group for IFD (Tab. II). Additional risk factors for development of IFD are as follows: neutropenia >10 days; treatment with corticosteroids at a therapeutic dose of ≥0.3 mg/kg for ≥3 weeks in the past 60 days; immunosuppressive therapy during the past 90 days; treatment with recognized B-cell immunosuppressants (e.g., ibrutinib); and graft--versus-host disease (GVHD) [1].

Table I. Grading system

Strength of Recommendation (SoR)	Definition
Grade A	Strong support of a recommendation for use
Grade B	Moderate support of a recommendation for use
Grade C	Marginal support of a recommendation for use
Grade D	Support for a recommendation against use
Quality of Evidence (QoE)	**Definition**
Level I	Evidence from at least 1 properly designed randomized, controlled trial (oriented on the primary end point of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (including secondary end points), without randomization; from cohort or case controlled analytic studies (preferably from >1 centers; from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Definitions of invasive fungal disease

In 2002, with subsequent modifications in 2008 and 2019, the Infectious Diseases Group of the EORTC and the MSG presented the definitions and classification of invasive mycoses, distinguishing the diagnoses of confirmed, probable, and possible IFD, based on the results of diagnostic tests [1, 19, 20]. Published autopsy data indicate that ante-mortem diagnosis of IFD has currently reached 50% of cases. With respect to the level of diagnosis, the current updated classification includes proven, probable, and possible IFD (Tab. III) [1].

Updated 2019 criteria for diagnosis of proven IFD include [1]:

Yeast infection

1. Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells, e.g., *Cryptococcus* spp., indicating encapsulated budding yeasts, or *Candida* spp., showing pseudohyphae or true hyphae.
2. Recovery of a yeast specimen by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process.
3. Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* spp.) or yeast-like fungi (e.g., *Trichosporon* spp.).
4. Amplification of fungal DNA by polymerase chain reaction (PCR), combined with DNA sequencing, when yeasts are seen in formalin-fixed paraffin-embedded tissue.
5. Cryptococcal antigen in cerebrospinal fluid (CSF) or blood confirms cryptococcosis.

Mold infection

1. Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy, in which hyphae or melanized yeast-like forms are seen, accompanied by evidence of associated tissue damage.
2. Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically/radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage (BAL) fluid, a paranasal or mastoid sinus cavity specimen, and urine.
3. Blood culture that yields a mold (e.g., *Fusarium* spp.) in the context of a compatible infectious disease process.
4. Amplification of fungal DNA by PCR, combined with DNA sequencing, when molds are seen in formalin-fixed paraffin-embedded tissue.

Diagnostics

The diagnosis of fungal infection should be based on the entire picture, taking into account risk factors, clinical symptoms, and results of radiological and microbiological tests. The most common signs of IFD are fever, which persists for more than 5–7 days despite the use of broad-spectrum antibiotic therapy, and clinical symptoms of respiratory infection. In any case of suspected IFD, the presence of the fungus should be demonstrated by direct microscopic assessment and/or culture and/or histopathological examination, which is a direct evidence of invasive mycosis but often requires the use of invasive procedures such as BAL or biopsy of the affected tissue. However, the BAL result does not differentiate fungal invasion from colonization.

Imaging

High-resolution computed tomography (HRCT) enables early diagnosis of IPA and has prognostic significance. The most characteristic feature of angio-IPA is the “halo” sign in HRCT; atypical infiltrative nodular lesions are often observed and are difficult to interpret, and the image with the “air crescent” is a late radiological symptom. The radiological picture of IFD of the paranasal sinuses and the CNS in both CT and magnetic resonance imaging (MRI) is not characteristic. Pulmonary abnormalities such as tree-in-bud opacities and interstitial abnormalities are excluded from the clinical features as they can be due to a wide range of pathologies in addition to IFD [1].

Table II. Risk groups for development of invasive fungal disease

High risk	ALL, AML, SAA, MDS, CGD, SCID, allo-HCT
Low risk	Auto-HCT, patients with other malignancies undergoing chemotherapy

Table III. Definitions of invasive fungal disease

Level of diagnosis	Definition
Proven	Histopathologic, cytopathologic, or direct microscopic examination or positive culture of a specimen obtained by needle aspiration or biopsy, including blood sample. The category of proven IFD can apply to any patient, regardless of whether the patient is immunocompromised
Probable	Probable invasive fungal disease requires the presence of at least 1 host factor, a clinical feature, and mycologic evidence (Tab. IV), and it is proposed for immunocompromised patients only
Possible	Cases that meet the criteria for a host factor and a clinical feature but for which mycological evidence has not been found are considered possible IFD. (1,3)-β-D-glucan (BDG) is not considered to provide mycological evidence of any invasive mold disease. The possible category is proposed for immunocompromised patients only, except for endemic mycoses

Imaging: pediatric distinctness

Radiographic findings are less specific in children than those reported in adults. Chest CT scans in children with proven IPA commonly show nonspecific changes and not the halo sign, air crescent formation, or cavitation seen in adults [1].

Galactomannan (GM) assay

Among the serological tests, the GM assay is validated for the diagnosis of IA. For high-risk neutropenic patients, it is recommended that serum GM should be determined twice a week, with a positive test result ≥ 0.5 in two consecutive tests. This marker can also serve as an indicator of response to antifungal therapy. The GM examination in BAL is useful in the pulmonary diagnostics of IA in patients with and without neutropenia. Index GM > 1.0 in BAL is regarded as positive, while in the CSF, GM ≥ 0.7 in single or ≥ 0.5 in two tests is considered positive. In patients treated with antimold antifungals, the GM index can be false negative; in this cohort, negative GM does not exclude the possibility of IFD.

Mannan determination

The clinical value of mannan test results is currently regarded as low due to difficulties in interpretation. Currently, it is not regarded as distinctive [1].

β-D glucan (BDG) determination

BDG is a component of the cell wall of yeast and mold fungi. The presence of BDG in serum confirms IFD but does not differentiate among aspergillosis, candidiasis, and fusariosis. False-positive and false-negative test results limit its practical application in the diagnosis of mold fungi. Currently, BDG is not considered to provide mycological evidence of any invasive mold disease [1].

PCR analysis

Progress in standardization has increased the value of PCR, which is now recommended with the use of international standardization. Systematic reviews of *Aspergillus* PCR methods for blood and BAL fluid conclude that PCR provides a robust diagnostic test for screening and confirming the diagnosis of *Aspergillus* infection [1, 18].

Biomarkers: pediatric distinctness

There are also far fewer data to support the clinical use of non-culture-based fungal biomarkers in children, although the GM assay performs similarly in children and adults when used as an adjunctive tool to diagnose IA. Likewise, there are few data regarding the use of BDG, *Candida* mannan antigen, and anti-mannan antibody biomarkers in pediatrics. Recent data support the utility of BDG in the CSF for the diagnosis and therapeutic monitoring of children with *Candida* meningoencephalitis, but data regarding the utility of PCR assays and the T2Candida assay for diagnosis are sparse [1].
Diagnostics of IFD should be focused on the presence of clinical (imaging) and microbiological (culture, biomarkers) evidences in patients with risk factors and symptoms and signs of infection (Tab. IV).

Therapy

The strategy of prophylaxis and antifungal treatment was developed as part of the ECIL as a result of cooperation of experts from the European Society for Blood and Marrow Transplantation (EBMT), EORTC, European LeukemiaNet, and the International Immunocompromised Host Society (ICHS). The principles of antifungal prophylaxis, empirical therapy, and preemptive therapy; treatment of confirmed mycoses based on ECIL guidelines and the IDSA recommendation system; as well as medicines available and registered in Poland, are presented below.

Antifungal prophylaxis

Adults

Antifungal prophylaxis in adults with acute leukemias

Patients with AML treated with intensive chemotherapy should receive posaconazole in prophylaxis of IFD (Tab. V). The drug is effective in reducing the rate of IA and influences the survival (Grade AI). Posaconazole should be given as oral suspension (po)

Table IV. Clinical and microbiological evidences of IFD

Clinical evidences	Suggestive imaging: pulmonary HRCT, CT/MRI of sinuses, abdominal CT/MRI, CNS MRI and/or neutropenic fever not resolving or recurrent in spite of use of broad-spectrum antibiotics for at least 72 hours and/or signs and symptoms of septic shock in neutropenic patient
Microbiological evidences	Biomarkers (GM, rarely cryptococcal antigen) and/or PCR for fungi: positive and/or histopathologic examination for fungi: positive and/or blood culture and/or culture of biologic specimen from normally sterile site: positive for fungi

Table V. Recommendations for antifungal prophylaxis in adults

Antifungal	Acute leukemia	HCT: neutropenic phase		GVHD phase
		Low-risk IMD	High-risk IMD	
Fluconazole, iv/po	BI	AI	DII	DII
Posaconazole, po (TDM)	AI	BII	BII	AI
Voriconazole, iv/po (TDM)	BII	BI	BI	BI
Micafungin, iv	BI	BI	CI	CII
LAmB/ABLC, iv	CII	CII	CII	CII
Itraconazole (capsules)	DII	DII	DII	DII

TDM – therapeutic drug monitoring; LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex

(3 × 200 mg) or intravenously (iv) (2 × 300 mg on the first day, followed by 1 × 300 mg daily) until neutropenia recovery. In the ALL setting, prophylaxis with fluconazole (400 mg/day, iv/po) or micafungin (50 mg/day, iv) is advisable.

Antifungal prophylaxis in adults after HCT

For lower-risk HCT recipients (HCT from matched sibling donor, low incidence of mold IFD in the center) during neutropenia, fluconazole is recommended for antifungal prophylaxis with monitoring of GM and possibly HRCT (Grade AI). Micafungin (50 mg/day, iv), with a broader spectrum of antifungal activity than fluconazole, is also effective (Grade BI). Itraconazole – available in Poland only in the form of capsules – is not recommended for prophylactic use, as opposed to the oral solution or intravenous form.

In higher-risk HCT patients (HCT from mismatched/unrelated donor, high rate of mold IFD in the center), use of voriconazole 2 × 200 mg po (2 × 400 mg on the first day) may be considered (Grade BI). Due to drug interactions, second-generation azoles should not be used during high-dose chemotherapy.

After hematopoietic reconstitution, in patients treated for GVHD, posaconazole (Grade AI) is the most effective in preventing IA. Secondary antifungal prophylaxis involves the prevention of IFD reactivation in patients undergoing allo-HCT.

Children

Antifungal prophylaxis in children with high risk for IFD development

Effective antimold prophylaxis should be used in patients with risk for IFD development (Grade BII, Tab. II). The therapy of choice in Poland remains posaconazole oral suspension (Grade BI). Its twice-daily body-weight-based dosing algorithm has been proposed by Welzen et al. [21] (Tab. VI) [21]. Alternatively, for pediatric patients, from 1 month to 12 years of age, a starting dose of posaconazole 6 mg/kg three times daily may be used [22]. Parallel administration of proton-pump inhibitors (PPIs) (omeprazole) and/or *Vinca* alkaloids should be avoided during posaconazole prophylaxis. Temporary withdrawal of azole prophylaxis is obligatory when a patient is given *Vinca* alkaloids (data from US clinical trials suggest a minimum of 24 hours of withdrawal before and after administration of *Vinca* alkaloids, but this has not been confirmed, yet). Micafungin in the dose 1 mg/kg/day might be an alternative for posaconazole (liver function should be monitored). Fluconazole prophylaxis (dose: 8–12 mg/kg/day) may be considered (Grade CI), but one should remember that this azole is effective mainly against *Candida albicans* (Tab. VII). To consider fluconazole prophylaxis, children have to fulfill two conditions: (1) they cannot be colonized by non-*albicans Candida* species (i.e., *C. glabrata*, *C. krusei*); (2) GM has to be monitored twice weekly due to the inefficiency of fluconazole against molds.

Antifungal prophylaxis in children undergoing allo-HCT: neutropenic phase (preengraftment)

Primary antifungal prophylaxis is recommended in children undergoing allo-HCT in neutropenic phase until engraftment (Grade BII). Therapeutic options include fluconazole (effective only against selected yeasts), micafungin, posaconazole, or voriconazole. Voriconazole dosing is presented in table VIII (according to the summary of product characteristics (SPC)). Due to several drug–drug interactions, azoles (except for fluconazole) should not be used during high-dose chemotherapy.

Antifungal prophylaxis in children undergoing allo-HCT: post-engraftment phase

In the absence of GVHD, antifungal prophylaxis should be continued after engraftment until immune recovery. In the presence of GVHD treated with augmented immunosuppressive therapy, prophylaxis against mold and yeast infections is recommended (Grade AII). The available options are posaconazole (Grade BI) and voriconazole (Grade BI).

Table VI. Posaconazole dosing algorithm for children

Body weight (kg)	Dosing in mg	Dosing in mL
10–14	2 × 120	2 × 3
15–19	2 × 160	2 × 4
20–24	2 × 200	2 × 5
25–29	2 × 220	2 × 5.5
30–34	2 × 260	2 × 6.5
35–39	2 × 280	2 × 7
≥40	2 × 300	2 × 7.5

Table VII. Recommendations for antifungal prophylaxis in children

Drug	High-risk group	Allo-HCT, neutropenic phase	Allo-HCT, GVHD	Auto-HCT	Secondary prophylaxis
Posaconazole	++	+	++		+
Micafungin	+	+		+	
Fluconazole	+	+		+	
Voriconazole		+	+		+

Antifungal prophylaxis in children undergoing auto-HCT

Fluconazole as primary prophylaxis against *Candida albicans* should be considered. Micafungin or caspofungin may be considered in patients with *C. glabrata*/*C. krusei* colonization.

Antifungal prophylaxis in children with low risk for IFD development (Tab. I)

Antifungal prophylaxis is recommended in selected patients with additional risk factors.

Secondary antifungal prophylaxis in children

Secondary antifungal chemoprophylaxis is recommended, targeted against the previous fungal pathogen, for as long as the patient is neutropenic or immunosuppressed (Grade AII). Either posaconazole or voriconazole may be considered.

Empirical antifungal therapy

IFD is often the cause of morbidity and mortality among high-risk febrile neutropenic patients. Although the diagnostic procedures have improved, accurate diagnosis of IFD remains difficult and is often delayed. Empirical antifungal therapy applies to patients in neutropenia with isolated fever that lasts more than 3–4 days despite broad-spectrum antibiotic therapy and is widely used in practice in hematologic and transplant centers, despite the lack of evidence in randomized trials for its effectiveness.

Empirical antifungal therapy must be considered in high-risk neutropenic patients who have persistent (or recurrent) fever after 72 hours of broad-spectrum antibiotic therapy and no identified infection source (Grade BII) [11, 18, 23, 24].

The choice of agent for empiric antifungal therapy depends mostly on previous antifungal prophylaxis. In patients receiving fluconazole prophylaxis, mold infections or fluconazole-resistant *Candida* spp. are the most likely causes; therefore, liposomal/lipid formulations of amphotericin B, echinocandins (Grade AI) or voriconazole (Grade BI) are indicated (Tab. IX). In patients who have been receiving posaconazole or voriconazole prophylaxis, the drugs of choice are liposomal/lipid formulations of amphotericin B (Grade AI) [25–28]. For patients who have not been receiving antifungal prophylaxis, *Candida* spp. are the most likely cause of invasive fungal infection, and the best option of empiric therapy comprises the echinocandins (caspofungin, micafungin) (Grade AI) [25–28]. Additionally, echinocandins are preferred in patients who have no obvious sites of infections, while voriconazole or amphotericin B preparations are preferred in patients with pulmonary infiltrates that are caused most probably by mold infection (Tab. X).

In empirical treatment, liposomal amphotericin (3 mg/kg, iv), caspofungin (70 mg, iv, on the first day, then 50 mg, iv) or micafungin (100 mg/day, iv) (Grade AI) have the highest recommendations.

Table VIII. Voriconazole dosing

Intravenous formulation	Loading dose	Maintenance dose
Adults	2 × 6 mg/kg on first day	2 × 4 mg/kg
Children 2–12 years and 12–14 years old with bw < 50 kg	2 × 9 mg/kg on first day	2 × 8 mg/kg
Children 12–14 years old with bw >50 kg and children 14–18 years	As in adults	As in adults
Oral formulation	**Loading dose (should be given intravenously)**	**Maintenance dose**
Adults with bw ≥40 kg	2 × 400 mg, iv, on first day	2 × 200 mg
Adults with bw <40 kg	2 × 200 mg, iv, on first day	2 × 100 mg
Children 2–12 years and 12–14 years old with bw < 50 kg	2 × 9 mg/kg, iv, on first day	2 × 9 mg/kg (max. 2 × 350 mg)
Children 12–14 years old with bw >50 kg and children 14–18 years	As in adults	As in adults

bw – body weight

Table IX. Summarized recommendations for empirical antifungal therapy

Antifungal	Adults	Children	Comments
Caspofungin	AI	AI	Not active against Mucorales
LAmB	AI	AI	
ABLC	BI	BI	Infusion-related toxicity
Voriconazole	BI		Not active against Mucorales and selected *Candida*
Micafungin	AI		
Itraconazole	DI		Not active against Mucorales and selected *Candida*
Fluconazole	CI		Not active against *Aspergillus* and selected *Candida*
D-AmB	DII	DII	
Combination therapy	DIII	DIII	

LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex; D-AmB – amphotericin B deoxycholate

Lipid amphotericin (5 mg/kg, iv) (Grade BI) is also acceptable, while amphotericin deoxycholate (D-AmB; 0.5–1 mg/kg/day, iv) is contraindicated due to toxicity (Grade DII).

Taking into account the increasing prevalence of mucormycosis, it is important to remember that echinocandins and voriconazole have no activity against molds. If mucormycosis is suspected, a liposomal/lipid amphotericin B formulation or isavuconazole should be given [12].

Regarding the toxicity of antifungal drugs, both caspofungin and voriconazole induce nephrotoxicity and severe infusion-related events significantly less often as compared to amphotericin B formulations, whereas patients receiving voriconazole have more episodes of transient visual changes and hallucinations. Among the mentioned antifungal drugs, echinocandins have the best toxicity profile and show lower potential to interact with other drugs [28, 29, 30].

Empirical antifungal therapy in children

Empirical antifungal therapy, when selected as a strategy, should be started after 72 hours of fever and continued until resolution of neutropenia. Empirical therapy can be considered in children with acute leukemia, after HCT, with GVHD, or undergoing immunosuppressive treatment from any other cause. Antifungals recommended for empirical therapy in children are caspofungin, LAmB, ABLC, or voriconazole. Switch in antifungal class is necessary in case of previous antifungal prophylaxis. If fluconazole was used in prophylaxis, then echinocandins, LAmB, or voriconazole can be used in empirical therapy. When voriconazole or posaconazole was used in prophylaxis, then LAmB is the drug of choice in empirical therapy.

Preemptive antifungal therapy

The alternative to empirical treatment strategy is diagnostic test-guided preemptive antifungal therapy. Preemptive therapy involves initiating antifungal therapy based upon the results of serial screening with GM, BDG, PCR assays, or pulmonary CT/HRCT scan [11, 18]. In most cases, it is defined by positive GM/PCR testing. It has been proved that in the preemptive strategy, the frequency of antifungal use and duration of therapy are significantly decreased as compared to the empirical strategy. The preemptive approach can result in more documented cases of IFD without compromise on survival and can be used as an alternative to empiric antifungal therapy, both in adults (Grade BII) and children (Grade BII) [18, 31]. It should be underlined that simultaneously with empiric or preemptive antifungal therapy, the greatest effort should be made to establish a proper diagnosis.

Therapy of invasive candidiasis

The most frequent species among yeasts is *Candida albicans*. However, an increase of infections caused by *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and – recently – *C. auris* is being observed, which is probably caused by wide prophylaxis with azoles. *C. krusei* is inherently resistant to fluconazole, and *C. glabrata* has variable susceptibility to fluconazole; thus, this compound is not recommended in these cases. The first-line antifungals in invasive candidiasis are caspofungin, micafungin, anidulafungin, and LAmB/ABLC, for *C. albicans, C. glabrata,* and *C. krusei* (Tab. XI). Voriconazole is also recommended against *C. krusei* species. Infections with *C. parapsilosis* should be treated with fluconazole or LAmB/ABLC. There are no clinical practice guidelines available for the management of *C. auris* in transplant patients, although empirical treatment with an echinocandin would be appropriate considering the reported susceptibility patterns [32].

A switch in class should be considered in patients with breakthrough infections on antifungal prophylaxis or empirical therapy (no grading) [13]. When the *Candida* species is azole-susceptible, step-down to fluconazole can be considered in stable patients after 5 days of iv therapy. In patients with *C. krusei* infection, switching to oral voriconazole is an option [12].

Table X. Empirical antifungal therapy in specific clinical situations

Clinical situation	Recommended	Not recommended
Previous azoles	LAmB, echinocandins	Azoles
Shock	LAmB, echinocandins	Azoles
Severe renal failure	Echinocandins, voriconazole (oral formula)	LAmB, fluconazole
Hepatic failure	Echinocandins, LAmB (weak recommendation)	Azoles

Table XI. Summarized recommendations for the management of candidiasis

Antifungal	*Candida* spp. (without identification)	*C. albicans*	*C. glabrata*	*C. krusei*	*C. parapsilosis*
Caspofungin	AII	AII	AII	AIII	BIII
Micafungin	AII	AII	AII	AIII	BIII
Anidulafungin	AII	AII	AIII	AIII	BIII
Voriconazole	BII	CIII		CIII	
Fluconazole	CIII	CIII			AIII
LAmB	AII	BII	BII	BII	BII
ABLC	BI	BII	BII	BII	BII
D-AmB	CII	CII	CII	CII	CII

LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex; D-AmB – amphotericin B deoxycholate

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

Catheter removal

Most recent studies suggest a beneficial effect of catheter removal on outcome. Early adequate therapy and removal of central venous line were independently associated with lower mortality [1, 33, 34]. The recommendation is to rapidly remove the catheter (Grade BII) irrespective of the *Candida* species. If the central venous catheter cannot be removed, treatment should include an echinocandin or a liposomal/lipid formulation of amphotericin B due to their better activity on *Candida* biofilms [12].

Duration of antifungal therapy in candidiasis

The optimal duration of therapy for uncomplicated candidemia is 14 days after blood cultures are sterile; resolution of signs and symptoms; and resolution of neutropenia. For tissue-invasive candidiasis, the duration of treatment is defined by the site, the patient's response, and resolution of predisposing disorders [13].

Therapy of invasive aspergillosis

Adults

Voriconazole and isavuconazole are currently recommended for the treatment of confirmed aspergillosis in first-line therapy (Tab. XII). Based on randomized studies, voriconazole has been shown to reduce mortality in IA compared to conventional amphotericin. Treatment should be started with an iv dose of 2 × 6 mg/kg on the first day, then 2 × 4 mg/kg. Monitoring of blood drug levels is recommended because of the variable nonlinear pharmacokinetics of voriconazole. The neurotoxic, hepatic, and ocular complications occurring during voriconazole therapy are reversible, but their occurrence requires discontinuation of the drug. Late complications relate to the risk of developing skin cancer. In 2016, the results of a prospective study confirmed the similar efficacy of isavuconazole and voriconazole in the treatment of IA [11]. Isavuconazole available in iv and oral forms is better tolerated than voriconazole [35]. Both liposomal and lipid amphotericin are effective in the treatment of IA, and their use should be considered in the case of azole resistance and intolerance, as well as in patients receiving second-generation azole prophylaxis (posaconazole, voriconazole). For the treatment of IA, D-AmB should not be used. Currently, D-AmB is considered to have no role in the treatment of IA when more-effective and less-toxic agents are available. Its limited efficacy and its poor safety profile led to a recommendation against its use [12].

Caspofungin, as monotherapy or in combination with voriconazole or amphotericin, or amphotericin monotherapy is proposed for second-line IA therapy. In some patients, there are indications for surgical intervention.

Surgical treatment

Surgical treatment is recommended in the cases of lesion contiguous to a large vessel, hemoptysis from a single lesion (embolization is an alternative), and localized extrapulmonary lesion, including CNS lesion. Additionally, decreasing the mass of fungal burden might be considered.

Duration of antifungal therapy in aspergillosis

It is not possible to define the time necessary for successful treatment of IA/IPA, and the range is 3–50 weeks. According to IDSA and ESCMID, it should be no shorter than 6–12 weeks [14, 15, 18]. It should be continued during immunosuppressive treatment until resolution of signs and symptoms. Patients after IA/IPA therapy should be given secondary prophylaxis when undergoing subsequent chemotherapy or any other immunosuppressive therapy. The European survey of the Infectious Diseases Working Groups of EBMT, ESCMID, EORTC, and Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne (SEIFEM) has shown that there is large variability between centers; however 6 and 12 weeks of treatment are the most often used lengths of therapy (Lanternier et al., submitted).

Table XII. Summarized recommendations for the management of aspergillosis in immunocompromised patients

Intervention	Adults	Children	Comments
First-line treatment			
Voriconazole	AI	AI	
Liposomal amphotericin B	AI	BI	
Isavuconazole	AI	No grading	Pediatric development ongoing in Phase II
ABLC	BII	BII	
D-AmB	DII	DII	
Combination therapy			
LAmB + Voriconazole	CII	CII	
LAmB + Caspofungin	CII	CII	

LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex; D-AmB – amphotericin B deoxycholate

Children

Voriconazole is the drug of choice in the treatment of possible, probable, and proven pediatric IA (Grade AI, Tab. XII). The loading dose and the first-week therapy should be via the iv route, and the use of oral formulations may be considered only in patients with documented clinical improvement. Voriconazole remains the current treatment of choice for infections involving the CNS. A switch in class is to be considered in patients with breakthrough aspergillosis on mold-active azole prophylaxis. Liposomal (Grade BI) or lipid (Grade BII) formulations of amphotericin B remain the first option if azole resistance is suspected or confirmed. Options for second-line treatment include LAmB in amphotericin-B-naive patients (Grade BI) and voriconazole in voriconazole-naive patients (Grade AI). Further options approved in children include caspofungin (Grade AII) and ABLC (Grade BII). One may consider combination therapy in the most severe cases. Either voriconazole or an amphotericin B product--plus-an echinocandin might be used for salvage treatment (Grade CII). Isavuconazole is a promising agent, which has proved its high efficacy in adults. The results of an ongoing Phase II trial on the use of isavuconazole in pediatric patients with aspergillosis are pending. Therefore, the pediatric recommendations for targeted aspergillosis therapy with isavuconazole have not yet achieved grading.

Therapy of invasive mucormycosis

Treatment of mucormycosis is comprehensive and should include treatment of the underlying disease, antifungal pharmacotherapy, and surgery. The importance of correcting diabetes and acidosis, treatment of granulocytopenia, reducing doses, or discontinuing steroids and/or other immunosuppressants is emphasized. As the first line, liposomal amphotericin in high doses (5–10 mg/kg) or, in cases without CNS involvement, lipid amphotericin (5 mg/kg) is recommended. Posaconazole or isavuconazole can be used as rescue therapy (Tab. XIII).

Surgical treatment

Surgical treatment is recommended whenever possible, particularly in rhino-orbito-cerebral, soft tissue, or localized pulmonary lesion involvement, and in disseminated presentation [36, 37].

Children

Surgical treatment is mandatory, if possible. Control of primary disease and comorbidities (e.g., diabetes) is essential. Drug of choice is LAmB or ABLC in high doses (LAmB 10 mg/kg; ABLC 7.5 mg/kg).

Duration of antifungal therapy in mucormycosis

Long-term treatment is necessary. Median duration of antifungal treatment in recent studies was 102 days, ranging from 27 days up to 735 days [38, 39].

Therapy of fusariosis

The taxonomic revision defined species complexes with similar physiological and molecular features within the genus *Fusarium*. Some of these plant pathogens cause opportunistic infections in humans: *Fusarium solani* species complex (FSSC), *F. oxysporum* species complex (FOSC), and *F. fujikuroi* species complex (FFSC) [40]. *Fusarium* keratitis and onychomycosis are the main manifestations in immunocompetent individuals, while involvement of other organs and disseminated disease are observed in neutropenic and immunosuppressed patients [40, 41].

Fusarium spp. possess intrinsic resistance to most antifungal agents with variable susceptibility to amphotericin B and extended-spectrum triazoles [40, 41, 42]. Based on available data, the European Fungal Infection Study Group (EFISG), the ESCMID, and the European Confederation of Medical Mycology (ECMM) recommend voriconazole (Grade AII) or liposomal/lipid formulation

Table XIII. Summarized recommendations for the management of mucormycosis in hematology/HCT patients

Intervention	Adults	Children	Comments
First-line treatment			
LAmB	AII	AII	
ABLC	BII	BII	
Posaconazole	BIII	BIII	
Combination therapy			
LAmB + Posaconazole	CIII	CIII	
LAmB + Caspofungin	CIII	CIII	
Second-line treatment			
Isavuconazole	AII	AII	
Posaconazole	BII	BII	
Combination therapy	BIII	BIII	
Adjunctive treatment			
Surgical debridement and drainage	AII	AII	Essential for favorable outcome
Reversal of immunosuppression	AII	AII	Improves the outcome
Granulocyte transfusion	CIII	CIII	Granulocytes as a protective factor; lack of solid data

LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex

of amphotericin B (Grade BII) for management of invasive fusariosis [43]. Posaconazole is advised as salvage therapy (Grade AII) [41, 43]. Summarized recommendations are presented in table XIV. When possible, immune defenses should be restored by immunosuppression tapering and granulocyte colony-stimulating factor (G-CSF) support (Grade AII) [40-43]. Granulocyte concentrate transfusion can be considered, especially in pediatric fusariosis (Grade CIII) [42, 43]. Antifungal treatment, combined with surgical debridement of infected tissues, is recommended in patients with hematological malignancies or undergoing HCT (Grade AII) [42, 43].

Therapy of scedosporiosis

The most virulent species of *Scedosporium* pathogenic for immunocompromised patients include *Lamentospora aurantiacum* (formerly *Scedosporium prolificans*) and *S. aurantiacum,* both predominant in hot countries, and *S. apiospermum,* predominant in areas with moderate temperature [43]. They may cause infection of any organ with a preference for the sinopulmonary area, skin, and the CNS. Disseminated scedosporiosis manifests with fever and positive blood culture in the majority of patients and can be associated with skin rash and focal CNS symptoms [41].

Scedosporium spp. belong to the most drug-resistant fungi, and no strong recommendation can be provided, especially in the case of *L. aurantiacum*. They demonstrate resistance to polyenes and reduced sensitivity to echinocandins; that is why a choice of treatment should be optimally driven by susceptibility testing [41]. According to EFISG/ESCMID/ECMM joint recommendations, voriconazole is the treatment of choice (Grade AII) with surgical debridement of the localized lesions (Grade AIII) [43]. Infections with *L. aurantiacum* are difficult to manage, and outcome may be improved by surgical excision of lesions, restoration of circulating polymorphonuclear and mononuclear leukocytes, and combined therapy with voriconazole plus terbinafine or other combination (Tab. XV).

Dosing of antifungals

The pharmacokinetics of antifungal drugs in children can vary from those in adults. The recommended dosing of antifungals in adults and children is shown in table XVI.

Table XIV. Summarized recommendations for the management of fusariosis [40–43]

Intervention	Recommendations	Comments
First- line treatment		
Voriconazole	AII	Therapeutic drug monitoring
LAmB	BII	Fungi resistance possible
ABLC	CIII	Limited case reports
Salvage therapy		
Posaconazole	AII	Therapeutic drug monitoring
Voriconazole	AIII	Therapeutic drug monitoring
Adjunctive treatment		
Surgical debridement	AII	Improve the outcome
Reversal of immunosuppression	AII	Improve the outcome
Granulocyte transfusion	CIII	With cautions in HCT patients

Recommendations for adults; can be applied to children; LAmB – liposomal amphotericin-B; ABLC – amphotericin B lipid complex

Table XV. Summarized recommendations for the management of scedosporiosis [41–43]

Intervention	Recommendations	Comments
First-line treatment		
Voriconazole	AII	Therapeutic drug monitoring
LAmB	CIII	Variable activity
Posaconazole	CIII	Case reports
Combination therapy*		
Posaconazole plus terbinafine	BIII	Case reports
Voriconazole plus terbinafine	BIII	Case reports
Voriconazole plus caspofungin	BIII	Case reports
Adjunctive treatment		
Surgical debridement and drainage	AIII	Essential for favorable outcome
Reversal of immunosuppression	AII	Improves the outcome
Granulocyte transfusion	CIII	Granulocytes as a protective factor; lack of solid data

**Disseminated or lung infection with Lamentospora auratiacum; recommendations for adults; can be applied to children; LAmB – liposomal amphotericin-B*

Table XVI. Recommended dosing of antifungals in adults and children

Antifungal drug	Dosing in adults	Dosing in children	Comments
Fluconazole	Prophylaxis: 50–400 mg, po/iv, qd Treatment: loading dose 400–800 mg, iv, qd on Day1, then 400 mg, iv, qd	8–12 mg/kg/day, iv/po	
Itraconazole	Prophylaxis: 200 mg, iv, qd on Day 1, followed by oral solution 200 mg Treatment: 200 mg, iv, qd		It is discouraged to use itraconazole in tablets, since bioavailability is poor. Only tablets are available in Poland – this formula is not recommended due to poor bioavailability
Posaconazole	Prophylaxis: 200 mg tid suspension, or 300 mg tablet qd Treatment: 200 mg qid or 400 mg bid suspension or 300 mg tablet bid on Day 1, followed by 300 mg qd	600–800 mg/day, po	In 2–4 daily doses. For children with bw < 40 kg, dosing as recommended in table VI Only suspension formula is reimbursed in Poland. Tablets are not available in Poland
Voriconazole	Loading dose of 6 mg/kg, iv, bid on Day 1, followed by 4 mg/kg, iv, bid. The recommended dosing of oral form is 200 mg bid	Loading dose: 2 × 9 mg/kg/day, iv Maintenance dose: 2 × 8 mg/kg/day	Detailed dosing data for children and adults are shown in table VIII
Isavuconazole	Loading doses of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours) via po (2 capsules) or iv administration, followed by 372 mg qd, po/iv, starting 12–24 hours after the last loading dose		
Anidulafungin	Loading dose of 200 mg, iv, on Day 1, then 100 mg, iv, qd	1.5 mg/kg/day, iv (Day 1: 3 mg/kg)	Not licensed for children
Caspofungin	Loading dose of 70 mg, iv, on Day 1, then 50 mg, iv, qd	50 mg/m^2/day, iv (Day 1: 70 mg/m^2)	Max: 50 mg/day (Day 1: 70 mg)
Micafungin	100–150 mg, iv, qd; no loading dose is required	1–4 mg/kg/day, iv	Dosing in prophylaxis: 1 mg/kg/day (>50 kg: 50 mg); therapeutic 2 mg/kg/day; dosing in infants: 4 mg/kg/day
Liposomal amphotericin B (LAmB)	5 mg/kg, iv, qd	3–5 mg/kg/day, iv	
Amphotericin B lipid complex (ABLC)	3–5 mg/kg, iv, qd	5 mg/kg/day, iv	
Amphotericin B deoxycholate	0.5–1 mg/kg, qd		It is discouraged to use this formulation of AmB
Flucytosine	4 × 25 mg/kg bw	4 × 25 mg/kg bw	In CNS cryptococcosis, in combination therapy with LAmB, for at least 14 days
Terbinafine	1 × 250 mg/day (tablet)		Not recommended for children (in SPC)

iv – intravenous; po – per os; d – day (24 hours); bw – body weight; qd – once daily; bid – twice daily; tid – three times daily

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Authors' contributions

JS, JGT, AW, KK, MB, LG – design of the study. JS, JGT, AP, KK, LG – writing the manuscript. All authors – analysis of recommendations, final approval.

Conflict of interest

JS has received lecture fees or has been a participant of meetings supported by Pfizer, MSD, Gilead, TEVA, and Astellas. KK has received lecture fees or has been a participant of meetings supported by Pfizer, MSD, Gilead, TEVA, and Astellas. JGT has received lecture fees or has been a participant of meetings supported by Pfizer, Novartis, and Celgene. TS has received lecture fees or has been a participant of meetings supported by Pfizer, Gilead, and TEVA. AP has been a participant of meetings supported by MSD and Pfizer. JS, JGT, AW, KK, MB, and LG participated in the Pfizer Advisory Board.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform requirements for manuscripts submitted to biomedical journals.

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