High risk of invasive fungal disease in children undergoing hematopoietic cell transplantation or complex anticancer therapy: adverse role of post-transplant CMV replication

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Abstract

Introduction: We analyzed the epidemiology and outcomes of treatment of invasive fungal disease (IFD) in children during anticancer therapy (PHO, pediatric hematology and oncology) or after hematopoietic cell transplantation (HCT) over a period of eight consecutive years in a single-center study.

Material and methods: Overall, a total of 254 HCTs were performed, and 415 children were newly diagnosed for malignancy. Incidence, epidemiology and outcome of IFD were analyzed.

Results: The cumulative incidence of any IFD was 32.6% in allogeneic hematopoietic cell transplantation (allo-HCT), 22.2% in PHO, and 6.0% in autologous hematopoietic cell transplantation patients (auto-HCT). The incidence of proven +probable IFD was 12.6%, 10.4%, and 6.0%, respectively. As many as 77.0% HCT and 67.4% PHO of fungal episodes occurred in acute leukemia patients: the highest incidence of any IFD was observed for acute lymphoblastic leukemia (29.3% in HCT; 40.5% in PHO) and for acute myeloblastic leukemia (51.1% in HCT; 65.0% in PHO) patients. There were no significant differences in the incidence of fungal infections in both allo-HCT and PHO patients between the 2-year periods. Factors contributing to an increased risk of IFD in allo-HCT patients were: cytomegalovirus replication, and acute and chronic graft-versus-host disease. Survival from IFD was 91.9% in PHO, and 78.1% in HCT patients. Fungal pneumonia in HCT patients resolved in 62.9%, while in PHO patients it resolved in 93.5%.

Conclusions: The risk of IFD in allo-HCT patients is much higher than in auto-HSCT and PHO patients. The outcome of IFD is better in PHO and auto-HCT than in allo-HCT settings.

Key words: fungal infections, malignant diseases, pediatric hematology and oncology, hematopoietic cell transplantation, children

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Introduction

Infections constitute a major problem in patients undergoing oncological treatment or hematopoietic cell transplantation (HCT) [1–4]. These complications can compromise the benefit of both anticancer therapy and transplantation. Oncological wards and transplant units are usually equipped with specific programs or guidelines for diagnostics, as well as for prophylactic, empirical, pre-emptive and targeted therapeutic management against bacteria, viruses, fungi and parasites [5–9]. To date, no strategy has proved entirely successful, and thus each center should be aware of its local infectious epidemiology.

In 2012, a nationwide program on infections in Polish pediatric hematology oncology (PHO) and transplant centers was initiated (acronym: iPhot) [10]. This program enabled assessment of the incidence and outcome of infections in PHO and pediatric HCT centers in various aspects [10–12], including differential analysis with the adult HCT population [13]. Results of multicenter analyzes based on the data from 2012–2017 have shown that the worst outcome was observed in cases of fungal infections, especially invasive fungal disease (IFD) in a transplant setting, both in children and adults [10, 13, 14]. These findings justify a focused approach to antifungal management based on the use of antifungal prophylaxis in subgroups of patients with the highest incidence of IFD, e.g. in patients undergoing allogeneic HCT (allo-HCT) or chemotherapy for acute leukemia.

In this context, we analyzed the epidemiology and outcome of treatment of IFD in a single-center pediatric study, updated for another two years.

Thus, the objective of this study was analysis of the incidence and outcome of fungal infections in children during anticancer therapy (PHO, pediatric hematology and oncology) or after HCT over a period of eight consecutive years in a single-center pediatric study.

Material and methods

Patients

All children newly diagnosed for malignancy or undergoing HCT during 96 consecutive months between 2012 and 2019 were included in the study: 415 patients with newly-diagnosed malignancies, and 254 patients after HCT [including 187 allo-HCT and 67 autologous hematopoietic cell transplantation patients (auto-HCT)].

Study design

Eight years of epidemiology and outcomes of IFD were analyzed. Data was collected on the basis of consecutive 2-year periods determined by the introduction of a national program of antifungal prophylaxis with the second generation of azoles: i.e. before prophylaxis (2012–2013),

a transitional period (2014–2015), a period with modern prophylaxis (2016–2017), and a continuation period. In 2012–2013 the study was retrospective, and from 2014 it was prospective.

Oncological treatment in acute leukemia

During the analyzed eight-year period, all patients with acute lymphoblastic leukemia (ALL) were treated with the Intercontinental Cooperative ALL-IC-2009 protocol up to 30 September 2018, and subsequently with the AIEOP-BFM-2017 protocol. Patients with acute myeloid leukemia (AML) were treated according to the Berlin-Frankfurt-Munster AML-BFM-2004 protocol up to 2014, and subsequently with the AML-BFM-2012 protocol.

Diagnosis of fungal infections

Diagnoses of IFD were made, according to the EORTC/MSG criteria, as proven, probable, or possible [15, 16]. All HCT and PHO patients were screened with a galactomannan test mainly during neutropenia, or on the basis of clinically-driven indications. Computed tomography (CT), including high-resolution CT (HRCT) or magnetic resonance imaging (MRI) of an area involved in infection, was performed also on the basis of clinical indications [17]. In cases of a new episode of fever, microbiological specimens were used for culture. Biopsy of involved tissue was made where this was possible and clinically justified [17, 18].

Anti-fungal management and supportive therapy

Standard uniform anti-infective prophylaxis, including an environmental prophylactic strategy, was applied to patients undergoing HCT [19–21]. Empirical, preemptive or targeted anti-fungal therapy was administered with various antifungal agents according to the current commonly accepted strategies [9, 17]. Antifungal prophylaxis was used routinely in allo-HCT patients during the neutropenic phase or immunosuppressive therapy, and usually included fluconazole or other azoles up to 2014. Subsequently, posaconazole or voriconazole was used in allo-HCT patients in cases of graft-versus-host disease (GvHD), and in patients with AML or high-risk ALL during conventional chemotherapy, as well as for secondary prophylaxis. In patients with ALL, prophylaxis with azoles was rarely used during the induction phase due to the potential risk of interaction with vincristine, leading to neurotoxicity and other adverse events. During the intensification/consolidation phase, antifungal prophylaxis was used between cycles of chemotherapy, while usually being temporarily withdrawn during chemotherapy with the use of non-azole antifungal in selected patients. Commercial intravenous immunoglobulins were administered monthly in cases of decreased serum immunoglobulin concentration after transplantation or oncological therapy until B-cell function recovery.

Antibacterial antibiotic prophylaxis was used in all HCT patients during neutropenia or immunosuppressive therapy, and included penicillin or cephalosporin or ciprofloxacine. Preemptive or targeted anti-viral therapy was applied according to commonly accepted strategies.

Infection-related mortality

Treatment-related mortality (TRM) was defined as any death occurring at any point after the start of treatment that did not occur as a result of relapse or secondary malignancy. Outcome of infection was regarded as positive in cases of survival from infection or negative in cases of death occurring with an infectious complication. For the purpose of this study, infection-related mortality (IRM) analysis was restricted to fungal infections, being defined as any death occurring in the presence of IFD, starting from the day of diagnosis of the infection. In cases of relapse or progression of malignancy, this event was regarded as the primary cause of death, regardless of any diagnosis of concomitant infection.

Ethics

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to, and that appropriate ethical review committee approval has been received.

Statistical analysis

Cumulative incidences of fungal infections were calculated using competing risk analysis, starting from the day of transplant in an HCT setting, or the day of cancer diagnosis in a PHO setting, to the day of the first infection. Death was considered as the competing event. For the purpose of cumulative incidence analysis, an event was defined as the diagnosis of a first specific infectious disorder. Non-categorical variables were compared with a Mann-Whitney U test, and categorical variables were compared with a chi-square test. Hazard risk (HR) and 95% confidence intervals (95% CI) were calculated for the difference in occurrence of infections in patients. The Kaplan-Meier method was used to determine survival from invasive fungal infection.

Multivariate models for the development of fungal infections were calculated using the logistic regression model. Variables analyzed in HCT patients included: age (≤10 years, >10 years); sex (female, male); donor source (matched sibling donor, MSD; mis/matched unrelated donor, MUD//MMUD); disease (acute leukemia, other); conditioning intensity (myeloablative, other); donor/recipient CMV serostatus (negative/negative, any positive); CMV replication (absent/present); acute GvHD occurring before infection onset (grade 0/1, grade 2–4); and chronic GvHD occurring before infection onset (no, yes). Use of anti-thymocyte globulin (ATG) was a variable dependent on alternative donor, as it was used almost exclusively in MUD/MMUD transplants.

The stepwise selection procedure was used to select significant covariates. All reported p-values are two-sided; p <0.05 was considered as statistically significant.

Results

Demographics

Over the analyzed period of 96 consecutive months, a total of 415 PHO patients were newly diagnosed for malignancy, including 121 with ALL, 20 with acute myeloblastic leukemia (AML), 35 with non-Hodgkin lymphoma (NHL), 39 with Hodgkin's disease (HD), 61 with central nervous system tumors (CNS), 20 with neuroblastoma (NBL), 17 with Wilms tumor (WT), 13 with Ewing sarcoma (ES), six with osteosarcoma (OST), 25 with rhabdomyosarcoma (RMS), 13 with germ cell tumors (GCT), and 25 with other solid tumors (ST). During this period, a total of 254 HCTs were performed including 187 allo-HCTs and 67 auto-HCTs. Children were transplanted due to ALL (n =82), AML (n =45), NHL/HD (n =19), MDS (n =10), bone marrow failure syndromes (BMF, n =25), primary immunodeficiency (PID, n =15), neuroblastoma (NBL, n =32), Ewing sarcoma (n =13), or other diseases (n =13) (Table I).

Incidence of infections

The cumulative incidence of fungal infections between 2012 and 2019 in PHO patients was 22.2% (95% CI =18.2–26.2), while in HCT patients it was 25.3% (95% CI =20.0–30.6) (p =0.214) (Figure 1). The overall risk of any

Table I. Primary diseases of analyzed patients

Variable	HCT	PHO
Total	254 (187 allo, 67 auto)	415
Acute lymphoblastic leukemia	82	121
Acute myeloblastic leukemia	45	20
Non-Hodgkin lymphoma	9	35
Hodgkin's disease	10	39
Solid tumors	58 (32 NBL, 13 ES, 13 other)	180 (61 CNS, 20 NBL, 17 WT, 13 ES, 6 OST, 25 RMS, 13 GCT, 25 other)
Other	15 PID, 25 BMF, 10 MDS	13 LCH, 2 CML, 2 MDS

HCT — hematopoietic cell transplantation; PHO — pediatric hematology and oncology; allo — allogeneic; auto — autologous; NBL – neuroblastoma; ES — Ewing sarcoma; CNS — central nervous system tumor; WT — Wilms tumor; OST — osteosarcoma; RMS — rhabdomyosarcoma; GCT — germ cell tumor; PID — primary immunodeficiency; BMF — bone marrow failure syndrome; MDS — myelodysplastic syndrome; LCH — Langerhans cell histiocytosis; CML — chronic myeloid leukemia
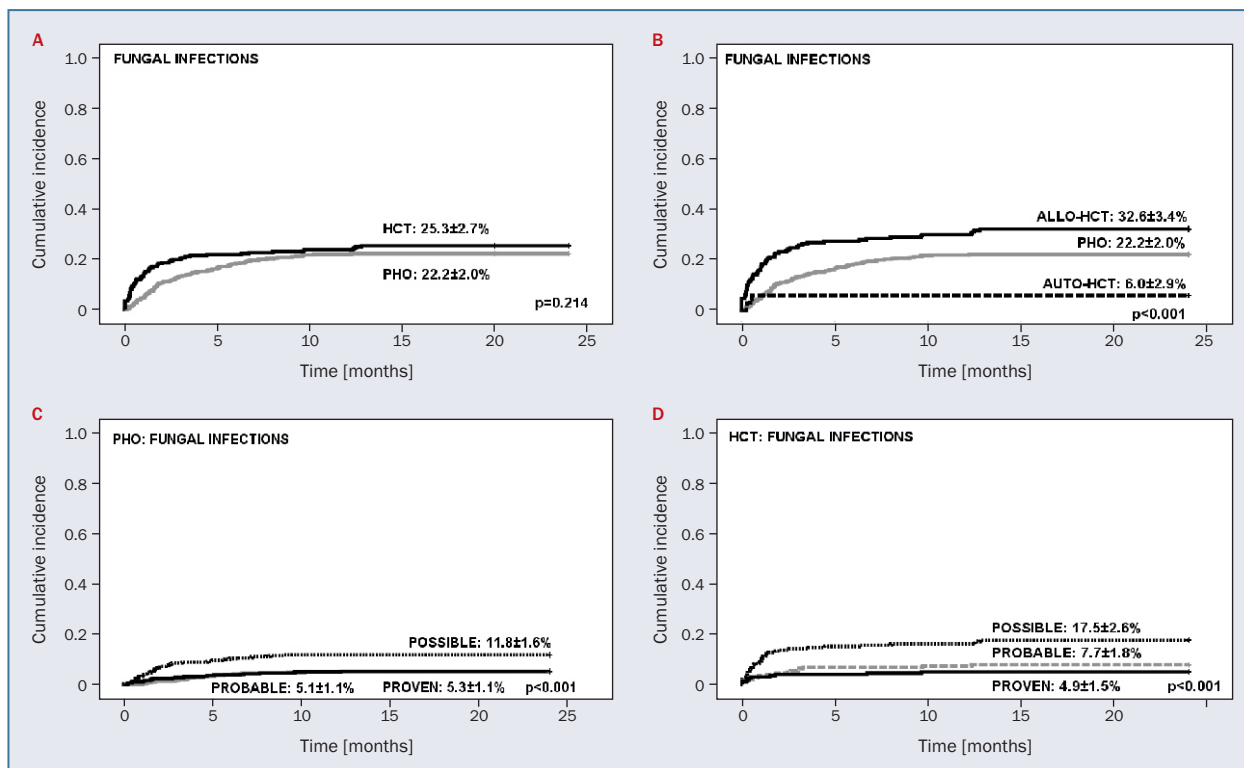
Figure 1. Cumulative incidence of invasive fungal disease (IFD): **A.** In pediatric hematology and oncology (PHO) versus hematopoietic cell transplantation (HCT); **B.** In PHO versus allogeneic hematopoietic cell transplantation (allo-HCT) versus autologous hematopoietic cell transplantation patients (auto-HCT); **C.** In PHO with respect to level of IFD diagnosis; **D.** In HCT with respect to level of IFD diagnosis

IFD in HCT (allo +auto) vs. PHO patients was similar: HR =1.2 (95% CI =0.8–1.7; *p* =0.357). Also, the risk of proven +probable IFD for HCT (allo +auto) vs. PHO was similar: HR =1.1 (95% CI =0.6–1.8; *p* =0.897). With respect to the type of transplant, the cumulative incidence of fungal infections was much higher after allo-HCT than after auto-HCT: 32.6% vs. 6.0% (HR =7.6, 95% CI =2.6–22.0; *p* <0.0001).

There were no significant differences in the incidence of fungal infections both in allo-HCT and PHO patients between the 2-year periods. Respective values for subsequent two-year periods for PHO vs. HCT were: 14.8% vs. 24.2% for 2012–2013 (*p* =0.092), 24.2% vs. 22.0% for 2014––2015, (*p* =0.8), 25.0% vs. 28.8% for 2016–2017 (*p* =0.4), and 25.7% vs. 26.0% for 2018–2019 (*p* =0.8).

The majority of fungal infections occurred within the first four months, and earlier after allo-HCT than in PHO patients after diagnosis of the malignancy. The median time to first fungal infection was shorter after allo-HCT than in PHO patients after diagnosis of malignancy: 2.2 months vs. 3.5 months, *p* <0.001. Due to sporadic infections after auto-HCT, a respective comparison was not carried out.

The overall risk of any IFD in allo-HCT vs. PHO patients was significantly higher up to day 100 (from transplant or cancer diagnosis, respectively): HR =2.3 (95% CI =1.5–3.5; *p* <0.001), and then lower after day 100: HR =0.5 (95% CI =0.3–1.0; *p* =0.073). The overall risk of proven +probable IFD in allo-HCT vs. PHO patients was significantly higher up to day 100 (from transplant or cancer diagnosis, respectively): HR =2.5 (95% CI =1.3–4.7; *p* =0.006), and then lower after day 100: HR =0.4 (95% CI =0.1–1.1; *p* =0.098).

The cumulative incidence of IFD among PHO patients was 22.2%, including proven IFD in 5.3%, probable in 5.1%, and possible in 11.8% of patients (Figure 2). As many as 67.4% of IFD episodes occurred in acute leukemia patients. IFD incidence was 40.5% among ALL patients (proven 8.3%, probable 10.7%, possible 22.3%), and 65.0% among AML patients (proven 15.0%, probable 5.0%, possible 45.0%). In other types of cancer, the incidence of IFD was: NHL 25.7%, RMS 12.0%, CNS 9.8%, NBL 20.0%, ES 7.7%, GCT 7.7%, WT 0%, osteosarcoma 0%, and other solid tumors 20.0%.

IFD incidence among allo-HCT patients was 32.6%, including proven in 4.9%, probable in 7.7%, and possible IFD in 17.5% patients (Figure 1). Altogether, 77% of the IFD cases were reported in acute leukemia patients. IFD incidence was 29.3% among ALL (proven 4.9%, probable 7.3%, possible 17.1%), and 51.1% among AML patients (proven 2.2%, probable 13.3%, possible 35.6%). The incidence of
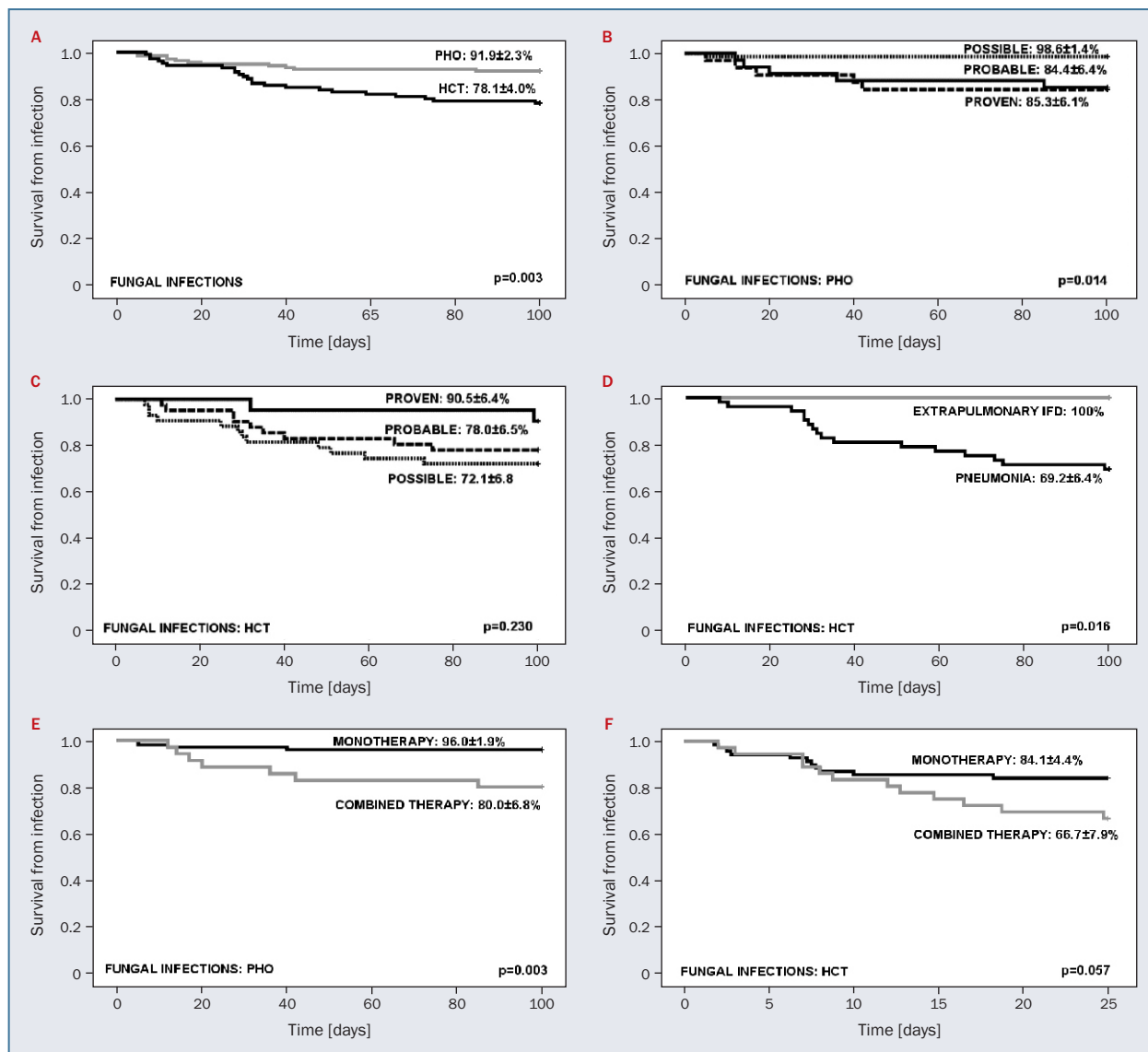
Figure 2. Survival from invasive fungal disease (IFD): **A.** In pediatric hematology and oncology (PHO) versus hematopoietic cell transplantation (HCT); **B.** In PHO with respect to level of diagnosis; **C.** In HCT with respect to level of IFD diagnosis; **D.** In HCT patients in pulmonary versus extrapulmonary IFD; **E.** In PHO with respect to antifungal monotherapy versus combined therapy; **F.** In HCT patients with respect to antifungal monotherapy versus combined therapy

IFD was 36.0% in BMF, 30.0% in MDS, and 13.3% in PID. Additionally, the incidence of IFD in auto-HCT was 6.3% in NBL, 11.1% in NHL, and 10% in HD.

The number of infections with respect to time periods is shown in Table II. Proven IFDs were diagnosed in 22 PHO and 13 HCT patients, with 25 and 13 identified fungal species, respectively (Table III). *Candida spp.* was the most prevalent causative factor, detected mainly as a blood-stream infection.

Risk factors of infections in allo-HCT patients

Factors contributing to an increased risk of fungal infections both in uni- and multivariate analysis were: CMV replication, and acute and chronic GvHD (Table IV). Fungal infections were also less likely after non-myeloablative or reduced-intensity conditioning, although this did not reach statistical significance.

Survival after fungal infections

Survival from IFD was 91.9% in PHO, and 78.1% in HCT patients. With respect to IFD level of diagnosis in PHO, patients with possible IFD had a 98.6% cure rate, while probable and proven IFD had comparable cure rates of 84–85% (Figure 2). In HCT patients, no significant differences were found in the cure rate, although possible IFD resolved in 72.1%, probable in 78.0%, and proven

Table II. Hazard risk of infections after hematopoietic cell transplantation (HCT) compared to pediatric hematology and oncology (PHO) patients with respect to time periods

Infections	Total	0–30 days	31–100 days	101–180 days	181–365 days	>365 days
allo-HCT (n =187)						
Total	61	33	17	2	5	4
Proven	9 (14.8%)	5 (15.2%)	2 (11.8%)	0 (0%)	2 (40.0%)	0 (5.0%)
Probable	16 (26.2%)	7 (21.2%)	7 (41.2%)	0 (0%)	1 (20.0%)	1 (25.0%)
Possible	36 (59.0%)	21 (63.6%)	8 (47.0%)	2 (100%)	2 (40.0%)	3 (75.0%)
auto-HCT (n =67)						
Total	4	4				
Proven	4 (100%)	4 (100%)				
Probable	0 (0%)	0 (0%)				
Possible	0 (0%)	0 (0%)				
PHO (n =415)						
Total	92	20	37	19	15	1
Proven	22 (23.9%)	5 (25.0%)	7 (18.9%)	4 (21.0%)	5 (33.3%)	1 (100%)
Probable	21 (22.8%)	1 (5.0%)	7 (18.9%)	9 (47.4%)	4 (26.7%)	0 (0%)
Possible	49 (53.3%)	14 (70.0%)	23 (62.2%)	6 (31.6%)	6 (40.0%)	0 (0%)
Hazard risk (allo-HCT vs. PHO) Total IFD	HR =1.7 95% CI =1.2–2.5 p =0.008	HR =4.2 95% CI =2.6–7.6 p <0.001	HR =1.0 95% CI =0.6–1.8 p =0.999	HR =0.2 95% CI =0.05– –0.97 p =0.053	HR =0.7 95% C =0.3–2.0 p =0.726	HR =9.0 95% CI =1.0–81 p =0.058
Hazard risk (allo-HCT vs. PHO) Proven/ /probable	HR =1.3 95% CI =0.8–2.3 p =0.341	HR =4.7 95% CI =1.7–12 p =0.002	HR =1.4 95% CI =0.6–3.4 p =0.533	HR =ND 95% CI =ND p =0.032	HR =0.7 95% CI =0.2–2.7 p =0.885	HR =2.2 95% CI =0.1–35 p =0.999

allo — allogeneic; auto — autologous; HR — hazard risk; CI — confidence interval; p — p-value; ND — not determined

in 90.5%. Fungal pneumonia in HCT patients resolved only in 62.9% vs. 100% in extrapulmonary involvement (p =0.016), while in PHO patients there were no differences: 93.5% vs. 88.4% (p =0.3). Antifungal monotherapy was related to a higher cure rate than combined antifungal treatment, both in PHO patients (96.0% vs. 80.0%, p =0.003), and HCT patients (84.1% vs. 66.7%, p =0.057). However, it should be noted that combined antifungal therapy was used in cases of a lack of improvement of initial therapy.

Discussion

This long-term study of the incidence and outcome of fungal infections in children during anticancer therapy (PHO) or after undergoing HCT in a single-center analysis has shown comparably high incidences of both any and proven +probable IFD in allo-HCT and PHO patients, and much lower incidence in auto-HCT.

In other studies, infections occur in overall 82% of children after allo-HCT [23], 21% after auto-HCT, and 49% with acute leukemia in a PHO setting [24]. With respect to HCT recipients, infections accounted for 13% of deaths after matched sibling donor HCT, 17% after unrelated donor HCT, and 7% after auto-HCT [25]. IFD was diagnosed in 12% of children within the first 30 days after allo-HCT [23], and was rare after auto-HCT [24]. In general, 53% all allo-HCT infectious deaths were caused by fungi, 20% by bacteria, 24% by viruses, and 3% by parasites [23], while deaths due to infections were rare after auto-HCT [24]. In analysis of autopsies, infections have been found to be the cause of death in 55% of adults

Table III. Etiology of proven fungal infections

Infection	PHO (25 species in 22 patients)	HCT (13 species in 13 patients)
Candida:		
• *albicans*	7	1
• *glabrata*	5	1
• *krusei*	1	1
• *parapsilosis*	1*	5*
• *dubliniensis*	3*	–
• *lusitaniae*	1*	–
• *guilliermonde*	2	–
Aspergillus:		
• *fumigatus*	2	1
• *flavus*	2	1
Other:		
• *Rhizopus mucoralis*	–	1
• *Lichteimia corymbifera*	–	1
• *Fusarium*	1	1

*Denotes fluconazole-sensitive strains of non-albicans *Candida;* PHO — pediatric hematology and oncology; HCT — hematopoietic cell transplantation

after allo-HCT, and in 18% after auto-HCT [26]. Overall, IFD, cytomegalovirus (CMV) and bacteria are the main non-relapse risk factors for deaths after HCT [27, 28].

In this context, our analysis has shown a higher incidence of any IFD both in PHO and allo-HCT settings. However, when proven or probable IFDs are taken into account, the incidences are comparable to other international pediatric data. It remains unclear which is the real threat of IFD diagnosed on a 'possible' level, something which is being diagnosed in over 50% of IFD cases, both in PHO and allo-HCT settings. Surprisingly, the outcome of possible IFD, although non-significantly, was lower than probable or proven IFD in HCT patients. This was not the case in PHO patients. The proven worse outcomes of possible IFDs lead to the issue of diagnosis at the level of biomarkers, imaging and tissue biopsy.

Given that in the majority of cases the possible IFD was diagnosed in patients with pneumonia, based on clinical signs and symptoms, and computed tomography imaging, it must be underscored that invasive diagnostics in a pediatric population in such cases is very difficult. Neither bronchoscopy with broncho-alveolar lavage (BAL), nor lung biopsy, is a standard procedure yet in children after

Table IV. Risk factor analysis for fungal infections in allogeneic hematopoietic cell transplantation patients

Variable	Characteristics	Univariate analysis		Multivariate analysis	
		Frequency	*p*-value	RR (95% CI)	*p*-value
Sex	Female	25/76 (32.9%)	0.999	1	0.999
	Male	36/113 (31.9%)		1.0 (0.5–1.9)	
Age	<10 years	31/98 (31.6%)	0.967	1	0.972
	>10 years	30/91 (33.0%)		1.1 (0.5–1.7)	
Disease	Other	17/50 (34.0%)	0.946	1	0.985
	Acute leukemia	44/137 (32.1%)		0.9 (0.5–2.1)	
Donor	MFD	12/35 (33.3%)	0.934	1	0.921
	other	49/154 (31.8%)		0.9 (0.5–2.4)	
Conditioning	Myeloablative	52/145 (35.9%)	0.083	1	0.075
	RIC	9/44 (20.5%)		0.5 (0.2–1.1)	
CMV serostatus (recipient)	Negative	5/28 (17.9%)	0.121	1	0.098
	Positive	56/161 (34.8%)		2.4 (0.9–6.8)	
CMV replication	Negative	5/93 (5.4%)	<0.001	1	<0.001
	Positive	56/96 (58.3%)		24 (9–66)	
Acute GvHD ≥2	No	45/165 (27.3%)	<0.001	1	<0.001
	Yes	16/24 (66.7%)		5.3 (2.1–13)	
Chronic GvHD	No	1/158 (0.6%)	0.682	1	0.725
	Yes	10/11 (90.9%)		157 (91– >1,000)	
Any GvHD	No	35/154 (22.7%)	<0.001	1	<0.001
	Yes	26/35 (74.3%)		9.8 (4.2–23)	

p — *p*-value; RR — relative risk; CI — confidence interval; MFD — matched family donor; RIC — reduced-intensity conditioning; CMV — cyclomegavirus; GvHD — graft-versus-host-disease

allo-HCT, although both these diagnostic techniques are being performed more frequently nowadays.

Another surprising outcome of our study is the better survival after antifungal monotherapy than after combined therapy. In general, it has been proven that combination therapy is more successful than monotherapy in first-line therapy of IFD [29]. In our study, however, combination therapy was applied almost exclusively as the second-line treatment after a lack of improvement in first-line therapy. This aligns with national [17] and international recommendations [9].

Our study highlights the negative role of CMV replication as an adverse factor leading to increased incidence of IFD. This indirect effect of viral infection is also a risk factor of mortality after HCT [30, 31].

Antifungal prophylaxis introduced in HCT patients and in patients with acute leukemias in 2014–2015, slowed down the increase in incidence of fungal infections from 2016 onwards, although it did not stop it. Looking into possible activities, other options to improve the outcome of IFD might be: wider use of invasive diagnostics, treatment with reference antifungals according to recommendations [9, 17], use of minimally-invasive surgery in diagnostics and treatment [32, 33], or successful prophylaxis and treatment of viral infections preceding development of IFD [4, 34, 35]. New diagnostic methods and antifungals may appear.

The strengths of our study are the collection of all necessary clinical data, as well as uniform diagnosis and treatment of patients. The same factors also serve as limitations of our study, because a single-center study carries the bias of a specific approach and similar interventions performed in the majority of patients.

In conclusion, the risk of IFD in allo-HCT patients is much higher than in auto-HSCT and PHO patients. Most fungal episodes occurred in acute leukemia patients, in both the allo-HCT and PHO groups. As expected, the outcome of IFD was better in the PHO and auto-HCT setting than in the allo-HCT setting. Fungal infection-related mortality was highest in transplant patients with pneumonia.

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Authors' contributions

JS had primary responsibility for study design. JS and PG performed the analysis and wrote the manuscript. KC, MD, PG and JS collected data. All authors contributed to data analysis and interpretation, and critical revision of the manuscript.

Conflict of interest

All authors declare no conflict of interest related to this study.

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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; Uniform Requirements for manuscripts submitted to Biomedical journals.

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