Acta Haematologica Polonica 50(3) • September 2019 • 167–173 • DOI: 10.2478/ahp-2019-0027

sciendo

ORIGINAL RESEARCH ARTICLE/PRACA ORYGINALNA

journal homepage: https://content.sciendo.com/ahp

Infectious complications in children and adults with hematological malignancies

Article history:
Received: 14.07.2019
Accepted: 30.07.2019

Jan Styczyński*

Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Jurasz University Hospital nr 1, Bydgoszcz, Poland

Abstract

Infections are the main cause of morbidity and mortality in pediatric hematology and oncology (PHO) and hematopoietic cell transplantation (HCT) settings in children and adults. The analysis of incidence and outcome of bacterial, fungal, and viral infections in Polish PHO/HCT centers was performed over a period of 72 months (2012–2017). The summary of infections in 5628 patients with newly diagnosed malignancy and 971 HCTs is presented in this paper. Additionally, data of 650 pediatric HCTs from 2012 to 2015 were compared with the data of 3200 HCTs in adults. The risk of any infection per patient was higher in HCT vs PHO patients (2062/971 vs 7115/5628; 2.1 vs 1.3; HR=1.7, p<0.0001). The incidence of bacterial infections was 34,2±0,6% in PHO vs 41,5±1,6% in HCT patients, and the outcome was better in PHO patients: 97,9±0,2% vs 91,8±1,0%. The incidence of patients with fungal infection was 8,8±0,4% vs 21,2±1,3%, and the outcome was better in PHO patients: 95,9±0,7% vs 85,8±2,3%. Incidence of viral infections was 5,0±1,0% in PHO setting, including part of previously transplanted patients, and 47,8±2,2% in HCT setting (60,9±2,3% allo-HCT; 5,6±1,3% auto-HCT). In children, the incidence was higher for bacterial (36.0% vs 27.6%), fungal (25.3% vs 6.3%), and viral (56.3% vs 29.3% allo-HCT; 6.6% vs 0.8% auto-HCT) infections than in adults (p<0.0001), and the outcome was better for bacterial (95.5% vs 91.4%), fungal (88.0% vs 74.9%), and viral (98.6% vs 92.3%) infections. In conclusion, the presented large studies have determined the incidence of infectious complications and their outcomes in HCT and PHO centers in Poland.

Keywords:
bacterial infections, invasive fungal infections, viral infections, malignant diseases, oncohematology

Introduction: nationwide project

Infections are the main cause of morbidity and mortality in patients with cancer or undergoing stem cell transplantation [1]. Children and adults with hematologic malignancies are especially susceptible to bacterial, fungal, and viral infections due to abnormality of the basic mediators of immunity. Factors that predispose these patients to infection include the following: alterations of the body's natural barriers, presence of central venous catheters, alteration of the innate immune system and acquired immunity, as well as intensive oncologic and supportive therapy.

The objective of this paper is to review the results of initiative of Polish Society of Pediatric Oncology and Hematology and Polish Society of Hematology and Blood Transfusion to collect data on bacterial, fungal, and viral infections in pediatric hematology, oncology (PHO) and hematopoietic stem cell transplant (HCT) units. Over a period of 72 months (2012–2017), data of infections in 5628 patients with newly diagnosed pediatric malignancy and 971 pediatric HCTs performed in participating centers were analyzed. Patients were also analyzed in chronological 2-year subgroups. Additionally, data of 650 HCTs from 2012 to 2015 were compared with the data of 3200 HCTs in adults.

Definitions

Classification of infections. Infections during neutropenia were classified as follows: (1) microbiologically documented infection (MDI) when pathogenic microorganism was recovered; (2) clinically documented infection (CDI) with the presence of signs and symptoms of inflammation at anatomic sites and non-recovered pathogen; and (3) fever of unknown origin (FUO) in case of fever without a localized source of infection or identified pathogen [2]. Severe and very severe neutropenia were defined by the peripheral blood absolute neutrophil count (ANC) below $0.5x10^9$/L and $0.2x10^9$/L, respectively.

Infectious episodes. Following episodes were reported: microbiologically documented bacterial infections; proven/probable/possible IFI; and latent and sporadic viral infections.

Fungal infections. The diagnosis of IFD was made according to EORTC/MSG criteria as proven, probable, or possible [3–5]. All HCT and PHO patients were screened with galactomannan test mainly during neutropenia or on the basis of clinically driven indications.

Viral infections: They were classified as episodic (diagnosed on the basis of clinical manifestation and supplemented with appropriate tests) or latent (requiring monitoring at the molecular level) [6–8]. Following latent viruses were included in the analysis: cytomegalovirus (CMV);

* Corresponding author: Jan Styczyński, Department of Pediatric Hematology and Oncology, Jurasz University Hospital, Collegium Medicum UMK, Curie-Sklodowskiej 9 Street, Bydgoszcz 85-094, Poland, e-mail: jstyczynski@cm.umk.pl

Epstein-Barr virus (EBV); varicella-zoster virus (VZV); human herpes virus 6 (HHV6); polyoma BK virus (BKV); and episodic viruses as follows: influenza (FLU), CARV (community-acquired respiratory virus, parainfluenza (PIF), metapneumovirus (MPV), respiratory syncytial virus (RSV)), and adenovirus (ADV). According to European Conference on Infections in Leukemia (ECIL) recommendations, preemptive approach was introduced for infections with two latent viruses: CMV and EBV [7,8]. PCR-based analysis was used for diagnosis of viral infections of material derived from blood, urine, or cerebrospinal fluid. CARV viruses were detected by PCR from respiratory swabs or bronchoalveolar lavage.

Prophylaxis of infections

Commonly accepted standard strategies have been applied for all patients undergoing HCT for prophylactic, empirical, and targeted anti-infectious therapy with various agents. The same policies of preemptive approach and anti-infectious prophylaxis were applied in all participating pediatric HCT centers. Empirical, preemptive, or targeted anti-infectious therapy was performed with various antibacterial, antiviral, and antifungal agents according to the commonly accepted strategies [7–13]. Antibacterial antibiotic prophylaxis was used in all centers routinely in neutropenia in PHO and all HCT patients and included penicillin, cephalosporin, or ciprofloxacin. Antifungal prophylaxis was used in all centers routinely in allo-HCT patients during neutropenic phase or immunosuppressive therapy and included fluconazole or, rarely, other azoles up to 2014, and then posaconazole or voriconazole was used in pediatric allo-HCT patients in GVHD phase or for secondary prophylaxis, as well as in AML or high-risk ALL during conventional chemotherapy in PHO setting. Acyclovir was used in prophylaxis of HSV and VZV infection at least until 1-year post-transplant. Weekly screening for DNA-emia and preemptive treatment were performed for EBV and CMV reactivation, according to European ECIL recommendations. Prevention of *Pneumocystis jiroveci* infection included cotrimoxazole after hematopoietic recovery until the end of neutropenia, end of immunosuppressive treatment and in all patients with acute leukemia during chemotherapy. A commercial immunoglobulin preparations were given in case of decreased immunoglobulin concentration during the first month after HCT and then monthly until B-cell function recovery. Most of the patients receiving myeloablative conditioning were commenced on gut rest from the first 5 days after HCT and received total parenteral nutrition until hematopoietic recovery. Environmental prophylaxis was applied in all HCT and PHO centers [14].

Overall incidence of infections in pediatric HCT vs PHO settings

A total number of 9177 confirmed infectious episodes were reported. The incidence was higher in HCT patients (n=971) than in PHO patients (n=5628) for bacterial (41.5% vs 34.2%, HR=1.4, 95% CI=1.2–1.6, p<0.0001), proven/probable/possible fungal (21.2% vs 8.8%, HR=2.8, 95% CI=2.3–3.3, p<0.0001), proven/probable IFI (9.5% vs 3.0%, HR=3.3, 95% CI=2.5–4.3, p<0.0001), and viral (47.8% vs 5.0%, HR=22, 95% CI=18.5–26.4, p<0.0001) infections [15]. The incidence of viral infections varied largely between allo-HCT (60.9%; 451/741) and auto-HCT (5.6%; 13/230). The risk of any infection per patient was higher in HCT vs PHO patients (2062/971 vs 7115/5628; 2.1 vs 1.3; HR=1.7, 95% CI=1.5–1.8, p<0.0001) (Fig. 1.). Overall results on incidence and outcome of infections during the first analyzed period were published previously [16].

Infections in pediatric hematology and oncology setting

Acute lymphoblastic leukemia (ALL)

The analysis included 1363 patients, with newly diagnosed ALL (2012–2017). The patients received therapy according to the ALL IC-BFM 2002 and 2009 (Intercontinental Berlin-Frankfurt-Munster Study Group) protocols [17].

Bacterial infections. Overall, 1511 episodes of bacterial MDI episodes were diagnosed in 726 out of 1363 (53.2%) children during chemotherapy. The number of bacterial episodes was 1–28 per person. The overall survival of patients who experienced >1 event was lower than survival of those who suffered 1, but no statistically significant difference. The most common site of bacterial infection was bloodstream (n = 518; 71.3%), followed by gastrointestinal tract (n = 443; 61%) and urinary tract (n = 245; 33.7%). Overall, 298/518 (57.5%) Gram-positive and 199/518 (38.4%) Gram-negative isolates were recovered from the bloodstream. In all, 20 children (2.75%) died due to sepsis, including six patients (2.4%) in the first analyzed time period (2012–2013), and six (2.8%) and eight (3.1%) patients in the consecutive ones (2014–2015 and 2016–2017, respectively).

Fungal infections. A total number of 406 episodes in 278/1363 (20.4%) children were reported as having a fungal infection during therapy of ALL, including 41 probable, 28 proven, and 337 possible, ranging from 1 to 7 per patients. The proven IFD was diagnosed in lungs (10 patients), gastrointestinal tract (7 patients), blood (7 patients), central nervous system (CNS) (3 patients), and eye socket (1 patients). Eight children (2.9%) died due to IFD: three proven and five possible IFD. The median time from ALL diagnosis to death was 4.4 months (range: 1–16.6).

Viral infections. 251/1363 (18.4%) children experienced a viral infection documented by PCR test. In total, 304 episodes of viral infections were identified: 1–4 per person. Five patients (2.0%) died due to viral infections. Two children (2.9%) died from CMV and AH1N1 co-infection, one (0.8%) due to AH1N1, and two (3.2%) due to CMV and RSV co-infection. The median time from diagnosis of ALL to death was 9.1 months (4.6–10.8).

Acute myeloid leukemia (AML)

In the study of the epidemiology and profile of bacterial infections (BI), invasive fungal disease (IFD) and viral infections (VI) in 250 children with initial AML (iAML) and 61 with relapsed/refractory (rAML) [18].

Infectious episodes. In 162 patients with primary AML, there were 504 episodes of BI (3.1 EIC per patient) while 49 episodes of IFD in 26 patients (1.9 EIC per patient) and 39 episodes of VI in 29 patients (1.4 EIC per patient). In 33 patients with rAML, there were

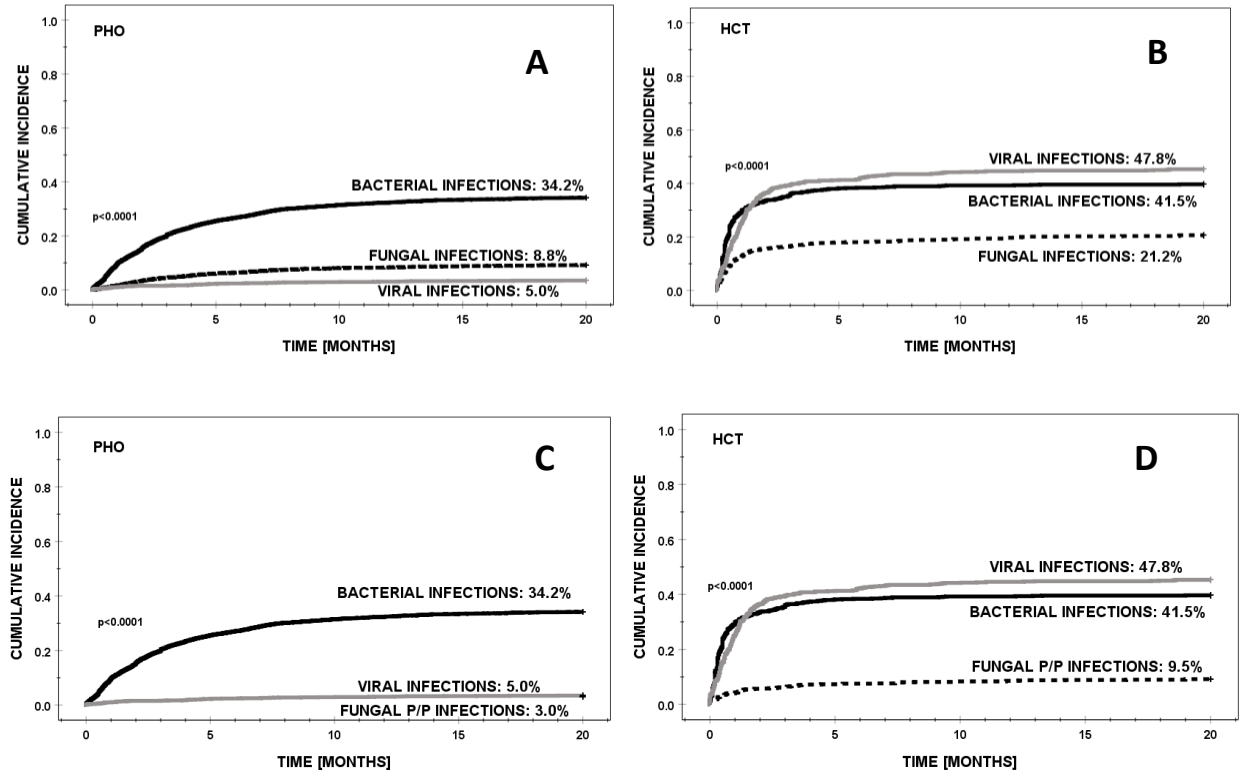

Fig. 1. Overall cumulative incidence of infections in pediatric hematology and oncology (PHO) and pediatric hematopoietic stem cell transplantation (HCT) settings between 2012 and 2017: (A and B) including possible, probable, and proven IFD; (C and D) including probable and proven but not possible IFD

78 episodes of BI (2.4 EIC per patient; p=0.2) while 14 episodes of IFD in nine patients (1.6 EIC per patient; p=0.8) and seven episodes of VI in seven patients (1.0 EIC per patient; p=0.8).

Incidence. In iAML group, overall, 592 episodes of infectious complications (EIC) were recorded in 190 (76.0%) patients (3.1 EIC per patient). Out of these 592 EIC, 504 (85.1%) were classified as bacterial infections (BI), 49 (8.3%) as proven/probable IFD, and 39 (6.6%) as VI. Similarly, in 41 (67.2%) patients with rAML disease, 99 EIC were found (2.4 IC per patient), including BI in 78 (78.8%), probable IFD in 14 (14.1%), and VI in 7 (7.1%) cases (p=0.5). Gram-negative strains were predominant, including multidrug-resistant strains in half of the cases. Characteristics of IFD and VI were comparable for iAML and rAML.

Survival of infectious complications. Overall, in iAML group, 10 out of 250 (4.0%) patients died due to EIC: IFD contributed to three deaths, whereas BSI caused by Enterobacteriaceae and Pseudomonaceae to three and two deaths, respectively. Among rAML group, 6 out of 61 (9.8%; p=0.08) patients died due to IC caused mainly by BSI of Enterobacteriaceae. The survival from infection was significantly lower in patients with rAML. The cumulative incidence of infection-related mortality was 6.1±2.0% for iAML and 12.2±5.0% for rAML (p=0.045).

HD and NHL

Infectious episodes. Among 129 lymphoma patients, there were 350 EIC, thus 282/350 (80.6%) episodes of BI, 39/350 (11.1%) episodes of VI, and 29/350 (8.3%) episodes of IFD. Bacterial EIC were predominant in B-NHL patients; 131/282 (46.5%) episodes of BI occurred in 56 patients, while in 26 LBL patients 65/282 (23.0%) BI episodes were observed, and in 3 ALCL children 11/282 (3.9%) episodes, and in 43 HL children 75/282 (26.6%) episodes [19].

Incidence. During the period of analysis in the group of 328 patients treated for lymphoma, at least one EIC was diagnosed in 129/328 (39.3%) children (including 51 girls, 78 boys, with median age 10.9 years), thus 86/167 (51.5%) NHL and 43/164 (26.2%) HL patients (p=0.002). BI were found in 85/167 (50.9%) NHL and in 43/164 (26.2%) HL children (p=0.003). VI were diagnosed in 20/167 (12.0%) NHL and 11/164 (6.7%) HL patients (p=0.2). Diagnosis of probable/proven IFD was made in 17 children, including 14/167 (8.4%) NHL and 3/164 (1.8%) HL patients (p=0.2).

Sites of bacterial infections. GI 96/282 (34.0%) and BSI 90/282 (31.9%) episodes predominated; UTI were diagnosed in 44/282 (15.6%), SSTI in 20/282 (7.1%), and other sites in 32/282 (11.4%) of BI episodes. The most common bacteria found in GI was Enterobacteriaceae 45/96 (46.9%) among Gram-negative strains, and Clostridiaceae 31/96 (32.3%), among Gram-positive strains.

Survival from infections. The survival was 94.0% for BI, 74.1% for IFD, and 100% for VI (p=0.09). For BI, survival was similar for Gram-positive and Gram-negative strain (p=0.5). The overall survival of lymphoma patients with IC was comparable for different types of infections.

Bone tumors

Infectious complications in 70 children with Ewing sarcoma (ES) and 56 with osteosarcoma (OSA) showed that the risk of infection was 7.1-fold higher in patients with ES vs OSA. Bacterial infections occurred in 74.3% patients with ES and in 41.1% with OSA: 33.0% of bacterial episodes were diagnosed as bloodstream (BSI), 31.1% as gastrointestinal tract, and 30.1% as urinary tract infection. Infection-related mortality (IRM) from bacterial infection was 6% vs 15% in ES vs OSA patients, respectively. Other infections included 7.1% of IFD and 6.3% viral ones. All patients who have died from infection had BSI and were in neutropenia. Bacterial infection occurring ≥5 months since the beginning of chemotherapy was a risk factor for death [20].

Clostridium difficile infections

Clostridium difficile infection is one of the most common causes of nosocomial infectious diarrhea in children in PHO and HCT settings. Episodes of CDI occurred in 14% PHO patients. The incidence of CDI was higher in patients with hematological malignancies in comparison to that with solid tumors. Patients with acute myeloblastic leukemia had shorter time to episode of CDI than those with acute lymphoblastic leukemia. Patients over 5 years and treated for acute leukemia had more severe clinical course of disease in PHO group. In HSCT group, CDI occurred in 8% patients. The incidence of CDI was higher in patients transplanted for acute leukemia. The recurrence rate was 14.7% in PHO and 20.7% in HSCT patients. CDI incidence was highest in patients with hematological malignancies. Most of the patients experienced mild CDI [21].

Fungal infections in PHO patients

Incidence. IFD incidence among all pediatric patients treated for malignancy was 9.2%, including possible in 6.5%, probable in 1.6%, and proven IFD in 1.1%. Introduction of antifungal prophylaxis from 2014 to 2015 in selected groups of patients (AML and high-risk ALL) did not change significantly the incidence of IFD in this setting: from 10.2% in first period to 8.3% in the third one (ns). In AML patients, the incidence of proven/probable IFD decreased from 19.7% in the first period to 10.8% in the second and to 8.4% in last one, while possible IFD from 23.5% and 25.7% to 14.8% in respective periods of time. In ALL patients, proven/probable IFD ranged from 6.7% to 4.9% and 4.8% in respective periods; however, incidence of possible IFD increased from 6.3% to 9.8% and 19.1% in respective periods [15, 22].
Outcome. Success rate of treatment of IFD was 95.9% in pediatric malignancy patients. With respect to the level of diagnosis of IFD, the outcome was 94.3% for proven, 92.4% for probable, and 96.9% for possible IFD. The outcome was 96.2% for children with ALL and 93.4% with AML [15].

Bacterial infections in HCT pediatric patients

A total number of 273 episodes of BI were diagnosed in 113/308 (36.7%) HCT (92 allo-, 22 auto-) children with median age 7 years (range: 0.02–22). Index of bacterial infection (IBI) was calculated as a ratio of patients with at least 1 BI to all HCT patients who underwent this type of transplant during analyzed period of time. The risk of BI did not depend on the underlying disease, but only on HCT donor type and was the highest after MMUD-HCT procedure. Among allo-HCT recipients, the IBI was 0.4 (MSD-HCT 0.3; MUD-HCT 0.4; MUD-HCT 0.8; p=0.027) and in auto-HCT 0.3 per 1 patient. The profile of BI depended on the underlying disease and HCT type while it did not depend on the occurrence of acute GVHD. The major cause of infections after allo-HCT for hematological malignancies and bone marrow failures as well as after auto-HCT was Enterobacteriaceae, and G-positive bacteria in patients with primary immunodeficiencies [23, 24].

Fungal infections in HCT pediatric patients

Incidence. IFD incidence among pediatric HCT patients was 20.6%, including possible in 12.0%, probable in 5.3%, and proven IFD in 3.3%. Introduction of antifungal prophylaxis from 2014 to 2015 (in patients in early phase after HCT or with GVHD) resulted in significant decrease in incidence of IFD in HCT patients from 27.0% in 2012–2013 to 11.7% in 2016–2017 (p<0.001). In AML patients, the frequency of proven/probable IFD decreased from 19.2% in first period to 17.6% in second period and to 1.5% in the third one while possible IFD from 25.5% to 21.6% and 17.4% in respective periods. In ALL patients, the incidence of proven/probable IFD decreased from 17.9% to 12.7% and 1.4% in respective periods while possible IFD varied from 13.4% and 15.2% to 11.3% in respective periods [15, 22].
Outcome. Overall outcome of IFD was 85.8%. With respect to the level of diagnosis of IFD, the outcome was 90.2%, for proven, 76.9% for probable, and 88.7% for possible IFD. The outcome was 84.7% for children with ALL and 84.8% with AML [15].

Viral infections in HCT pediatric patients

Incidence. The cumulative incidence was 57.9% in allo-HCT and 4.8% in auto-HCT patients. More than one pathogen was diagnosed in 46.0% of allo-HCT patients. Cumulative incidence of viral infections was 28.9% for CMV, 23.8% for BKV, 22.7% for EBV, 10.7% for ADV, 5.0% for RV, 1.9% for FLU, 1.2% for VZV, 1.2% for HHV-6, 0.7% for RSV, 0.5% NV, 0.4% for PIF, 0.4% for RHINO, 0.3% for HSV, 0.1% for hMPV, 0.1% for PVB19, and 0.1% for HBV.
Survival. Success rates were 100% after FLU, HBV, VZV, HHV6, or RV infections, and lower in other types of infections: EBV (90.7%), ADV (93.8%), BKV (94.2%), and CMV (94.6%) [15, 25, 26].

Children versus adults: infections are more frequent and have better outcome in children

Incidence. Pediatric patients had 2.9-fold higher incidence of infectious complications than adults. Infections were diagnosed in 60.8% children and 35.0% adults, including 69.1% vs 63.5% in allo-HCT, and 33.1% vs 20.8% in auto-HCT patients, respectively. Bacterial infections were more frequent in children (36.0% vs 27.6%). In adults, G-negative bacteria were more frequent than G-positive (64.6% vs 44.8%). The incidence was higher in children also for IFD

(25.3% vs 6.3%), and viral infections both after allo-HCT (56.3% vs 29.3%) and auto-HCT (6.6% vs 0.8%).

Outcome. Pediatric patients had 2.5-fold better survival of infections than adults. Children had better survival from bacterial (95.5% vs 91.4%; p=0.0011), fungal (88.0% vs 74.9%; *p*<0.001), and viral (98.6% vs 92.3%; *p*=0.0096) infections. Infection-related mortality was lower in children (7.8% vs 18.4%; *p*<0.0001). No child died of infection after auto-HCT. In multivariate analysis, the risk factors for death from infection were following: adult vs children, diagnosis of acute leukemia, mismatched transplants, chronic GVHD, infection with Gram-negative bacteria, CMV reactivation, and also duration of infection >21 days [27].

Conclusions

Presented large studies have determined the incidence of infectious complications and their outcome in pediatric HCT and PHO departments, as well as adult HCT centers in Poland. Emerging data from Polish PHO and HCT centers indicate high incidence of infectious complications in these populations [28–30]. Although the rate of bacterial infections is similar to data reported from international centers both for children and adults, our data suggest that the incidence of IFD in pediatric ALL and AML both in PHO and HCT settings is much higher than it was recently anticipated. Viral infections occur in a high rate of allo-HCT pediatric and adult patients, thus might severely compromise the overall benefit of transplant.

Acknowledgments

All listed investigators and institutions participating in the program should be regarded as co-authors of this paper: Jan Styczyński, Krzysztof Czyżewski, Magdalena Dziedzic, Mariusz Wysocki (Katedra Pediatrii, Hematologii i Onkologii, Szpital Uniwersytecki nr 1 im. Antoniego Jurasza, Collegium Medicum, Uniwersytet Mikołaja Kopernika w Toruniu, Bydgoszcz); Patrycja Zalas-Więcek, Katarzyna Jachna-Sawicka, Eugenia Gospodarek (Katedra i Zakład Mikrobiologii, Szpital Uniwersytecki nr 1 im. Antoniego Jurasza, Collegium Medicum, Uniwersytet Mikołaja Kopernika w Toruniu, Bydgoszcz); Przemysław Gałązka (Department of Pediatric Surgery, Collegium Medicum, Nicolaus Copernicus University Toruń, Bydgoszcz); Olga Gryniewicz-Kwiatkowska, Agnieszka Kołodziejczyk-Gietka, Bożenna Dembowska-Bagińska, Danuta Perek (Klinika Onkologii, Instytut-Pomnik Centrum Zdrowia Dziecka, Warszawa); Katarzyna Semczuk, Ewa Romanowska, Katarzyna Dzierżanowska-Fangrat (Zakład Mikrobiologii i Immunologii Klinicznej, Instytut-Pomnik Centrum Zdrowia Dziecka, Warszawa); Małgorzata Salamonowicz (Katedra i Klinika Pediatrii, Hematologii i Onkologii, Uniwersytet Medyczny, Warszawa; Katedra i Klinika Transplantacji Szpiku, Onkologii i Hematologii Dziecięcej, Uniwersytet Medyczny, Wrocław). Jowita Frączkiewicz, Karolina Siewiera, Krzysztof Kałwak, Ewa Gorczyńska, Alicja Chybicka (Katedra i Klinika Transplantacji Szpiku, Onkologii i Hematologii Dziecięcej, Uniwersytet Medyczny, Wrocław); Anna Szmydki-Baran, Łukasz Hutnik, Michał Matysiak (Katedra i Klinika Pediatrii, Hematologii i Onkologii, Uniwersytet Medyczny, Warszawa); Edyta Podsiadły, Joanna Rogulska, Anna Chmielewska-Semkowicz, Urszula Demkow (Zakład Diagnostyki Laboratoryjnej i Immunologii Klinicznej Wieku Rozwojowego, Uniwersytet Medyczny, Warszawa); Agnieszka Zaucha-Prażmo, Joanna Zawitkowska-Klaczyńska, Jerzy Kowalczyk (Klinika Hematologii, Onkologii i Transplantologii Dziecięcej, Uniwersytet Medyczny, Lublin); Liliana Chełmecka-Hanusiewicz, Walentyna Balwierz (Klinika Onkologii i Hematologii Dziecięcej, Polsko-Amerykański Instytut Pediatrii, Uniwersytet Jagielloński Collegium Medicum, Kraków); Renata Tomaszewska, Tomasz Szczepański (Katedra i Klinika Pediatrii, Hematologii i Onkologii, Śląski Uniwersytet Medyczny, Zabrze); Olga Zając-Spychała, Jacek Wachowiak (Klinika Onkologii, Hematologii i Transplantologii Pediatrycznej, Uniwersytet Medyczny, Poznań); Ninela Irga-Jaworska, Ewa Bień, Elżbieta Drożyńska (Katedra i Klinika Pediatrii, Hematologii, Onkologii, Uniwersytet Medyczny, Gdańsk); Marcin Płonowski, Maryna Krawczuk-Rybak (Klinika Onkologii i Hematologii Dziecięcej, Uniwersytet Medyczny, Białystok); Tomasz Ociepa, Małgorzata Bartnik, Paweł Wawryków, Tomasz Urasiński (Klinika Pediatrii, Hematologii i Onkologii, Pomorski Uniwersytet Medyczny, Szczecin); Filip Pierlejewski, Wojciech Młynarski (Klinika Pediatrii, Onkologii, Hematologii i Diabetologii, Uniwersytet Medyczny, Łódź); Zuzanna Gamrot-Pyka, Mariola Woszczyk (Oddział Hematologii i Onkologii Dziecięcej, Chorzowskie Centrum Pediatrii i Rehabilitacji im. dr E.Hankego, Chorzów); Zofia Małas (Wojewódzki Specjalistyczny Szpital Dziecięcy, Oddział Hematologii i Onkologii, Olsztyn; Instytut Matki i Dziecka, Warszawa), Wanda Badowska (Wojewódzki Specjalistyczny Szpital Dziecięcy, Oddział Hematologii i Onkologii, Olsztyn); Agnieszka Urbanek-Dądela, Grażyna Karolczyk (Oddział Hematologiczno-Onkologiczny, Wojewódzki Specjalistyczny Szpital Dziecięcy, Kielce); Weronika Stolpa, Grażyna Sobol-Milejska (Oddział Onkologii, Hematologii i Chemioterapii, Klinika Pediatrii, Śląski Uniwersytet Medyczny, Katowice); Jolanta Goździk (Ośrodek Transplantacji Uniwersyteckiego Szpitala Dziecięcego w Krakowie, Katedra Immunologii i Transplantologii Klinicznej, Uniwersytet Jagielloński Collegium Medicum, Kraków); Joanna Klepacka (Zakład Mikrobiologii, Uniwersytecki Szpital Dziecięcy, Kraków); Jakub Musiał, Radosław Chaber (Klinika Onkohematologii Dziecięcej, Uniwersytet Rzeszowski, Szpital Kliniczny nr 2, Rzeszów); Sebastian Giebel (Department of Hematology, Cancer Center and Institute of Oncology, Gliwice); Joanna Drozd-Sokołowska, Anna Waszczuk-Gajda, Grzegorz W Basak (Department of Hematology, Medical University, Warszawa); Jarosław Dybko (Department of Hematology, Medical University, Wroclaw; Department and Clinic of Internal and Occupational Diseases, Hypertension and Clinical Oncology; Medical University, Wroclaw, Poland); Joanna Mańko, Marek Hus (Department of Hematology, Medical University, Lublin); Agnieszka Piekarska, Alicja Sadowska-Klasa (Department of Hematology, Medical University, Gdańsk); Patrycja Mensah-Glanowska (Department of Hematology, Collegium Medicum, Jagiellonian University, Kraków); Sławomira Kyrcz-Krzemień (Department of Hematology, Medical University of Silesia, Katowice); Monika Biernat (Department of Hematology, Medical University, Wrocław); Agnieszka Wierzbowska (Department of Hematology, Medical University, Łódź); Piotr Rzepecki (Department of Hematology, Military Institute of Medicine, Warszawa); Agnieszka Tomaszewska (Department of Hematology, Medical University, Warszawa; Department of Hematology, Institute of Hematology and

Transfusion Medicine, Warszawa); Kazimierz Hałaburda (Department of Hematology, Institute of Hematology and Transfusion Medicine, Warszawa); Monika Adamska, Lidia Gil (Department of Hematology, Poznan University of Medical Sciences, Poznań, Poland).

Authors' contributions/Wkład autorów

JS – the only author.

Conflict of interest/Konflikt interesu

Author has received lecture fees from MSD, Gilead, Teva, Astellas, and Fresenius; was participant of Advisory Board for Novartis, Biotests and Roche; was participant of scientific meetings supported by Gilead, MSD, Astellas, Roche, and Jazz.

Financial support/Finansowanie

No financial support.

Ethics/Etyka

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.

References
Piśmiennictwo

[1] Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 2010;363:2091-101.

[2] Gil L, Styczynski J, Komarnicki M. Infectious complication in 314 patients after high-dose therapy and autologous hematopoietic stem cell transplantation: risk factors analysis and outcome. Infection 2007;35:421-27.

[3] Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.

[4] De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813-21.

[5] Groll AH, Castagnola E, Cesaro S, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol 2014;15:e327-40.

[6] Marr KA. Delayed opportunistic infections in hematopoietic stem cell transplantation patients: a surmountable challenge. Hematology Am Soc Hematol Educ Program 2012;2012:265-70.

[7] Ljungman P, de la Camara R, Cordonnier C, et al. European Conference on Infections in L: Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 2008;42:227-40.

[8] Styczynski J, Reusser P, Einsele H, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant 2009;43:757-70.

[9] Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica 2013;98:1836-47.

[10] Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98:1826-35.

[11] Styczynski J, Gil L. Prevention of infectious complications in pediatric HSCT. Bone Marrow Transplant 2008;42:S77-81.

[12] Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3 – 2009 update. Bone Marrow Transplant 2011;46:709-18.

[13] Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P: Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. Clin Infect Dis 2013;56:258-66.

[14] Styczynski J, Tridello G, Donnelly JP, et al. Protective environment for hematopoietic cell transplant (HSCT) recipients: The Infectious Diseases Working Party EBMT analysis of global recommendations on health-care facilities. Bone Marrow Transplant 2018;53:1131-38.

[15] Styczynski J, Czyzewski K, Zajac-Spychala O, et al. Improved outcome and differential incidence of infectious complications in children treated for malignancies or undergoing hematopoietic cell transplantation: results of multicenter nationwide study in Poland. Pediatric Blood Cancer 2018;65:S546.

[16] Styczynski J, Czyzewski K, Wysocki M, et al. Increased risk of infections and infection-related mortality in children undergoing haematopoietic stem cell transplantation compared to conventional anticancer therapy: a multicentre nationwide study. Clin Microbiol Infect 2016;22:179, 179.e1-179.e10.

[17] Zawitkowska J, Drabko K, Szmydki-Baran A, et al. Infectious profile in children with ALL during chemotherapy: A report of study group for infections. J Infect Chemother 2019 (epub ahead of print).

[18] Zajac-Spychala O, Skalska-Sadowska J, Wachowiak J, et al. Infections in children with acute myeloid leukemia: increased mortality in relapsed/refractory patients. Leuk Lymphoma 2019:1-8 (epub ahead of print).

[19] Zajac-Spychala O, Wachowiak J, Szmydki-Baran A, et al. Infectious complications in children treated for hodgkin and non-hodgkin lymphomas in polish pediatric leukemia/lymphoma study group: incidence, epidemiology and etiology. Leuk Lymphoma 2019;60:124-32.

[20] Czyzewski K, Galazka P, Zalas-Wiecek P, et al. Infectious complications in children with malignant bone tumors: a multicenter nationwide study. Infect Drug Resist 2019;12:1471-80.

[21] Salamonowicz M, Ociepa T, Fraczkiewicz J, et al. Incidence, course, and outcome of Clostridium difficile infection in children with hematological malignancies or undergoing hematopoietic stem cell transplantation. Eur J Clin Microbiol Infect Dis 2018;37:1805-12.

[22] Styczynski J, Czyzewski K, Wysocki M, et al. Micafungin in invasive fungal infections in children with acute leukemia or undergoing stem cell transplantation. Leuk Lymphoma 2016;57:2456-59.

[23] Zajac-Spychala O, Wachowiak J, Pieczonka A, et al. Bacterial infections in pediatric hematopoietic stem cell transplantation recipients: incidence, epidemiology, and spectrum of pathogens: report of the Polish Pediatric Group for Hematopoietic Stem Cell Transplantation. Transpl Infect Dis 2016;18:690-98.

[24] Zaucha-Prazmo A, Kowalczyk JR, Drabko K, et al. Incidence of Infectious Complications in Children With Acute Lymphoblastic Leukemia Treated With Hematopoietic Stem Cell Transplantation. Transplant Proc 2017;49:2183-87.

[25] Styczyński J, Czyżewski K, Siewiera K, et al. Viral infections in children undergoing hematopoietic stem cell transplantation. Acta Haematol Pol 2015;46:312-17

[26] Styczyński J, Czyżewski K, Frączkiewicz J, et al. Viral infections in children undergoing hematopoietic stem cell transplantation: report 2016 of Polish Pediatric Infectious Working Group of Polish Society of Pediatric Oncology and Hematology. Acta Haematol Pol 2017;48:23-7

[27] Czyżewski K, Styczyński J, Giebel S, et al. Age-dependent determinants of infectious complications profile in children and adults after hematopoietic cell transplantation: lesson from the nationwide study. Ann Hematol 2019 (epub ahead of print; doi. org/10.1007/s00277-019-03755-2).

[28] Styczynski J, Debski R, Krenska A, et al. Role of HLA match on results of hematopoietic stem cell transplantations from unrelated donors in children with acute leukemia and bone marrow failure syndromes. Acta Haematol Pol 2017;48:48-53

[29] Hus I, Piekarska A, Roliński J, et al. Szczepienia ochronne u dorosłych chorych na nowotwory hematologiczne oraz u chorych z asplenią – zalecenia PTHiT i sekcji do spraw zakażeń PALG. Acta Haematol Pol 2018;49:93

[30] Piekarska A, Giebel S, Basak G, et al. Szczepienia ochronne u chorych dorosłych po przeszczepieniu komórek krwiotwórczych – zalecenia sekcji do spraw zakażeń PALG. Acta Haematol Pol 2017;48:1-9