



Age-dependent determinants of infectious complications profile in children and adults after hematopoietic cell transplantation: lesson from the nationwide study

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Abstract

Incidence and outcome of microbiologically documented bacterial/viral infections and invasive fungal disease (IFD) in children and adults after hematopoietic cell transplantation (HCT) were compared in 650 children and 3200 adults in multicenter cross-sectional nationwide study. Infections were diagnosed in 60.8% children and 35.0% adults, including respectively 69.1% and 63.5% allo-HCT, and 33.1% and 20.8% auto-HCT patients. The incidence of bacterial infections was higher in children (36.0% vs 27.6%; $p < 0.0001$). Infections with Gram-negative bacteria were more frequent than Gram-positives in adults (64.6% vs

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44.8%; $p < 0.0001$). Outcome of bacterial infections was better in children (95.5% vs 91.4%; $p = 0.0011$). The IFD incidence (25.3% vs 6.3%; $p < 0.0001$) and outcome (88.0% vs 74.9%; $p < 0.0001$) were higher in children. The incidence of viral infections was higher in children after allo-HCT (56.3% vs 29.3%; $p < 0.0001$), and auto-HCT (6.6% vs 0.8%; $p < 0.0001$). Outcome of viral infections was better in children (98.6% vs 92.3%; $p = 0.0096$). Infection-related mortality was 7.8% in children and 18.4% in adults ($p < 0.0001$). No child after auto-HCT died of infection. Adult age, mismatched transplants, acute leukemia, chronic GVHD, CMV reactivation, infection with Gram-negatives, and duration of infection > 21 days were risk factors for death from infection. In conclusion, pediatric patients have 2.9-fold higher incidence and 2.5-fold better outcome of infections than adults after HCT.

Keywords Hematopoietic cell transplantation · Children · Adults · Incidence · Outcome · Bacterial infections · Viral infections · Invasive fungal disease

Introduction

Infections are a significant cause of morbidity, mortality, and resource utilization after hematopoietic cell transplantation (HCT) in children and adults. Bacterial infections both after allo- and auto-HCT are known to be associated with high mortality and have become a public health problem of major concern worldwide due to antibiotic resistance. Invasive fungal disease (IFD) remains an important cause of morbidity and mortality after allo-HCT. The incidence of IFD has been reported at 9% after allo-HCT with mortality up to 50% of patients, especially after alternative donor transplantations [1–3]. Most studies have reported a high rate of viral infection after allo-HCT but not auto-HCT. High viral infection risk after allo-HCT is likely related to the delayed immune reconstitution after transplantation [4]. Recent EBMT (European Society for Blood and Marrow Transplantation) analysis showed that infections are responsible for 21.6% of deaths after allo-HCT and 11.0% after auto-HCT in all age groups together; however, the risk, types, and outcome of infections varied between age groups [5].

Infections occur in up to 82% of children [6–8] and adults [9–11] after HCT; however, large multicenter studies on incidence and outcome of bacterial, fungal, and viral infections are lacking. So far also no direct simultaneous comparison was made between children and adults.

In this study, we compared the incidence, type, and outcome of infections in pediatric and adult HCT centers in Poland in multicenter cross-sectional nationwide study. We analyzed also risk factors for the incidence and outcome of infections in 650 children and 3200 adults who received HCT.

Patients and methods

Design of the study All consecutive patients transplanted between 1.01.2012 and 31.12.2015 in 5/5 pediatric, and in 11/13, adult HCT Polish centers were included in the

retrospective study. Bacterial, fungal, and viral infections were reported biannually by each center and data were analyzed centrally.

Bacterial infections Among bacterial infections, only microbiologically documented (MDI) episodes were considered. Colonizations were not included into this analysis. MDI were diagnosed as bloodstream, gut, urinary tract, respiratory tract (broncho-alveolar lavage), and skin and soft tissue infections. Bacteria were analyzed with attention to resistance profile, such as ESBL (extended-spectrum β -lactamases: bacteria producing extended-spectrum β -lactamases), AmpC (AmpC β -lactamases: bacteria producing chromosomal cephalosporinase AmpC type), KPC (*Klebsiella pneumoniae* carbapenemase, *Enterobacteriaceae* producing carbapenemase KPC type) [12], MRSA/MRSE (methicillin-resistant *Staphylococcus aureus* or *epidermidis*), or VRE (vancomycin-resistant enterococci). Multidrug resistant (MDR) bacteria denote resistance to at least two antibiotics used in empiric therapy or resistance to at least three of antibiotic classes [13, 14].

Fungal infections The diagnosis of IFD was made according to EORTC/MSG criteria as proven, probable, or possible [15–17]. Patients were screened with galactomannan test mainly during neutropenia or on the basis of clinically driven indications. Diagnostics for *Pneumocystis jirovecii* pneumonia (PjP) was performed in case of clinical indications.

Viral infections Viral infections were classified as episodic (diagnosed on the basis of clinical picture, and supplemented with appropriate tests) or latent (diagnosed at molecular level). The following viruses were detected by PCR analysis: adenovirus (ADV), polyoma BKV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and community-acquired respiratory viruses (CARV) including influenza.

Supportive therapy Uniform, standard anti-infective prophylaxis has been applied for patients undergoing HCT.

Prophylactic, empirical, preemptive, or targeted anti-infectious therapy was performed with various antibacterial, antiviral, and antifungal agents according to commonly accepted strategies [13, 14, 18–21].

Prophylaxis of infections Environmental prophylaxis was applied in all centers according to commonly accepted policy [22]. In children, antibacterial prophylaxis consisted of oral penicillin or second-generation cephalosporin (from day –10, until neutrophil count $> 1 \times 10^9/L$ or end of immunosuppressive treatment) and oral gentamicin used from the beginning of conditioning until hematological recovery. Children received antifungal prophylaxis with fluconazole; from 2014, posaconazole was used in case of graft versus host disease (GVHD) or in secondary prophylaxis. In children under age of 12 years, the drug was used off-label [17] and administered according to body weight, as shown by Welzen et al [23]. In adults during neutropenia, fluoroquinolones were used for antibacterial prophylaxis and fluconazole in antifungal prophylaxis together with regular screening of serum galactomannan and computed tomography (HRCT/CT) in case of suspected IFD. Both in children and adults, acyclovir was used in prophylaxis of HSV/VZV infection until 1 year post-transplant. Weekly screening for DNA-emia and preemptive treatment were performed for CMV and EBV reactivation. Prevention of PjP included cotrimoxazole after hematopoietic recovery until the end of immunosuppressive treatment. Commercial immunoglobulin preparations were given in case of decreased immunoglobulin concentration during the first month and then monthly until B cell function recovery. Most of children receiving myeloablative conditioning (MAC) were commenced on gut rest from the first 5 days after HCT and received total parenteral nutrition (TPN) until hematopoietic recovery.

Types of transplants Transplants were divided as autologous and allogeneic from matched sibling donors (MSD) or unrelated donors: matched (MUD) or mismatched (MMUD). Most patients who underwent MUD/MMUD-HCT received antithymocyte globulin (ATG) [24].

Statistical analysis For analysis of incidence, infectious event was defined as the diagnosis of a first specific infectious disorder. Categorical variables were compared with the chi-square test, non-categorical variables were compared with the Mann-Whitney *U* test. Odds ratio (OR) and confidence intervals (95%CI) were calculated for the difference in occurrence of infections in patients. Cumulative 2-year incidences of bacterial, fungal, or viral infections were calculated using competing risk analysis [25], starting from the day of transplant to the day of the first infection. Death was considered as the competing event. Outcome of infection was regarded as positive in case of survival from infection or negative in case

of death from infection. Infection-related mortality (IRM) was defined as any death that occurred in the presence of infection, starting from the day of diagnosis of infection. Death from infection was diagnosed as of bacterial, fungal, or viral cause; however, in many cases of IRM, patients suffered from multiple infections, and clinically the most symptomatic infection was regarded as the primary cause of death. In case of relapse and progression of malignancy, this was regarded as the primary cause of death, regardless of concomitant infection. The Kaplan-Meier method was used to determine IRM, counting from the day of diagnosis of infection. The relationship between the binary outcome, infection incidence, or death from infection, and other variables, regarded as risk factors, were analyzed using multivariate logistic regression: hazard risk (HR) and 95%CI were calculated for each factor. All reported *p* values are two-sided; *p* < 0.05 was considered as statistically significant.

Results

Overall characteristics of infections

A total number of 395/650 (60.8%) children and 1120/3200 (35.0%) adults (OR = 2.9, 95%CI = 2.0–3.6; *p* < 0.0001) were diagnosed for bacterial/viral MDI or IFD, including 345/499 (69.1%) and 676/1070 (63.5%) patients, respectively, after allo-HCT, while 50/151 (33.1%) and 444/2130 (20.8%) respectively, patients after auto-HCT. Patient characteristics and number of infections are shown in Table 1.

Total number of infectious episodes was 3180, including 1399 in children (2.15 per patient) and 1781 in adults (0.56 per patient) (*p* < 0.0001). Also respective numbers of infections per patient were higher in children for bacterial (0.88 vs 0.37; *p* < 0.0001), fungal (0.38 vs 0.06; *p* < 0.0001), and viral (0.89 vs 0.13; *p* < 0.0001) episodes.

Bacterial infections

Incidence The 2-year incidence of bacterial infections was 36.0% for children and 27.6% for adult patients (*p* < 0.0001), including allo-HCTs (36.9% vs 41.1%, ns), and auto-HCTs (32.9% vs 20.8%; *p* < 0.0001) (Fig. 1a–c). These numbers were however comparable for specific primary diseases including acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia/myelodysplastic syndrome (AML/MDS), non-Hodgkin lymphoma/Hodgkin lymphoma (NHL/HD), and severe aplastic anemia (SAA). Only 12.9% adults with multiple myeloma (MM) after auto-HCT had bacterial infections (Table 2).

Infections with Gram-negative bacteria were more frequent than Gram-positive in adults (64.6%), but not in children (44.8%). The difference was highly significant (*p* < 0.0001; OR = 2.3, 95%CI = 1.8–2.7). The frequency of G-negative

Table 1 Characteristics of patients

| Characteristics | Children | Adults | <i>p</i> |
|---|----------------------------|---------------------------|----------|
| All patients | | | |
| Total | 650 | 3200 | |
| Allo-HCT | 499 (76.8%) | 1070 (33.4%) | < 0.0001 |
| Auto-HCT | 151 (23.2%) | 2130 (66.6%) | < 0.0001 |
| Acute lymphoblastic leukemia (ALL) | 153 (23.2%) | 211 (6.6%) | < 0.0001 |
| Acute myeloid leukemia (AML) | 98 (15.1%) | 472 (14.8%) | 0.8306 |
| Myelodysplastic syndromes (MDS) | 32 (4.9%) | 79 (2.5%) | 0.0006 |
| Non-Hodgkin lymphoma (NHL)/Hodgkin lymphoma (HD) | 50 (7.7%) | 803 (25.1%) | < 0.0001 |
| Severe aplastic anemia (SAA)/bone marrow failure (BMF) | 75 (11.5%) | 58 (1.8%) | < 0.0001 |
| Other | | | |
| Primary immunodeficiencies (PID) | 75 (11.5%) | | |
| Neuroblastoma (NBL) | 49 (7.5%) | | |
| Ewing sarcoma (ES) | 13 (2.0%) | | |
| Multiple myeloma (MM) | | 1308 (40.9%) | |
| Chronic myeloid leukemia (CML)/myeloproliferative neoplasms (MPN) | | 119 (3.8%) | |
| Other | 43 (6.6%) | 122 (3.8%) | |
| Patients with infections | | | |
| Total number of patients with infections | Children (<i>n</i> = 395) | Adults (<i>n</i> = 1120) | |
| Sex: male/female | 230 (58.2%)/165 (41.8%) | 634 (56.6%)/486 (43.4%) | 0.5758 |
| Age at HCT: median (range) [years] | 7.2 (0.1–18.0) | 50.1 (18.0–77.8) | < 0.0001 |
| Donor type | | | < 0.0001 |
| Sibling | 97 (24.6) | 224 (20.0) | |
| Mismatched related | 4 (1.0) | 2 (0.2) | |
| Unrelated | 244 (61.7) | 450 (40.2) | |
| Autologous | 50 (12.7) | 444 (39.6) | |
| Stem cell source | | | < 0.0001 |
| Peripheral blood (PB) | 243 (61.5) | 1058 (94.5) | |
| Bone marrow (BM) | 149 (37.7) | 62 (5.5) | |
| Cord blood (CB) | 3 (0.8) | 0 (0.0) | |
| TBI given: yes/no | 64 (16.2%)/331 (83.8%) | 170 (15.2%)/950 (84.8%) | 0.6282 |
| Reduced intensity/standard conditioning | 71 (18.0%)/324 (82.0%) | 157 (14.0%)/963 (86.0%) | 0.0585 |
| Acute GVHD: yes/no (including auto-HCT) | 92 (23.3%)/303 (76.7%) | 166 (14.8%)/954 (85.2%) | 0.0001 |
| Neutrophil engraftment by day + 100: yes/no | 378 (95.7%)/17 (4.3%) | 1067 (95.3%)/53 (4.7%) | 0.7273 |
| Time to neutrophil engraftment: median (range) [days] | 14.0 (8–51) | 16.0 (6–60) | < 0.0001 |
| Follow-up after HCT: median (range) [months] | 21 (0–48) | 19 (0–41) | 0.6924 |

Legend: *HCT*, hematopoietic stem cell transplantation; *TBI*, total body irradiation; *GVHD*, graft versus host disease

bacteria with MDR phenotype was 67.8% (158/233) in children and 47.9% (404/843) in adults (OR = 2.3; 95%CI = 1.7–3.1, $p < 0.0001$). The frequency of G-positive bacteria with MDR phenotype was 43.6% (125/287) in children and 40.1% (185/461) in adults (OR = 1.1; ns). Detailed etiology of G-negative and G-positive infections is presented in Tables 3 and 4.

Timing Median time from the day of HCT to bacterial infection was 0.20 months (range –0.2–20.6) in children and 0.23 months (range –0.3–36.9) in adults. Median time of therapy of bacterial infection was 14 days (range 1–196; quartiles 10–21) in children and 9 days (range 1–36; quartiles 8–14) in adults ($p < 0.0001$).

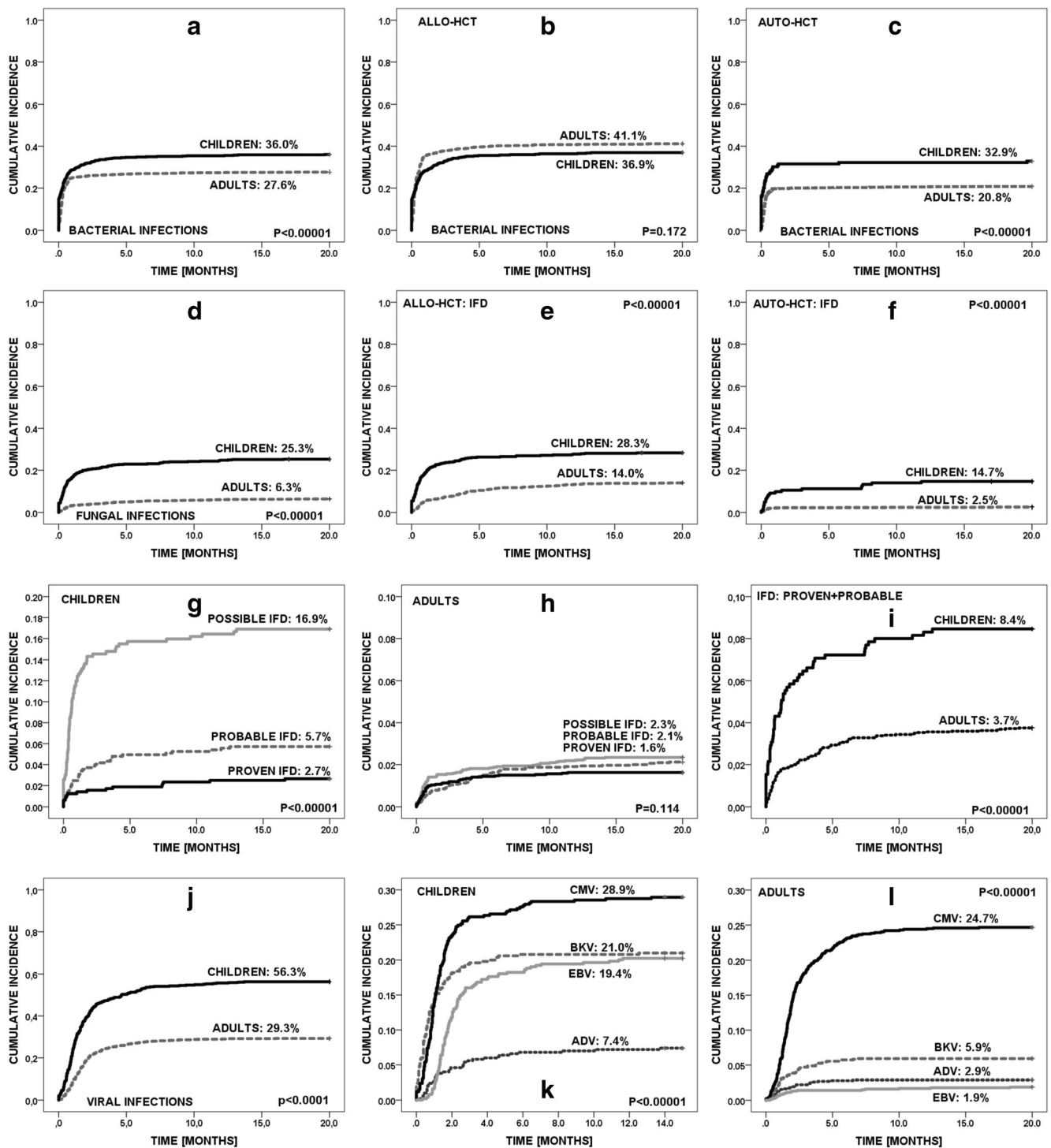


Fig. 1 Incidence of infections. **a** Total, **b** allo-, and **c** auto-HCT bacterial infections. **d** Total, **e** allo-, and **f** auto-HCT fungal infections. **g** Proven, **h** probable, and **i** possible IFD. **j** Total viral infections. **k**, **l** CMV, BKV, EBV, and ADV infections in children and adult

Risk factors In multivariate logistic analysis (Table 5), the risk of infections was higher after allo-HCT than auto-HCT (HR = 1.8; $p < 0.001$). In allo-HCT patients, the risk was higher in children (HR = 2.1; $p < 0.001$), in acute leukemia (HR = 1.6; $p < 0.001$), MUD vs MSD-HCT (HR = 1.6; $p < 0.001$), MMUD vs MSD-

HCT (HR = 2.0; $p < 0.001$), MAC (myeloablative conditioning) vs RIC (reduced-intensity conditioning) (HR = 1.3; $p < 0.001$), late (> 21 days) hematological recovery (HR = 3.3; $p < 0.001$), acute GVHD before infection (HR = 1.7; $p < 0.001$), and chronic GVHD before infection (HR = 1.4; $p = 0.014$). In auto-HCT

Table 2 Frequency of infections

| Parameter | Children | Adults | OR | <i>p</i> |
|-----------------------------------|-----------------|------------------|-----------------|----------|
| Bacterial infections | | | | |
| Total | 36.0% (234/650) | 27.6% (882/3200) | 1.5 (1.2–1.8) | < 0.0001 |
| Allo-HCT | 36.9% (184/499) | 41.1% (440/1070) | 0.8 (0.7–1.04) | 0.1093 |
| Auto-HCT | 32.9% (50/151) | 20.8% (444/2135) | 1.9 (1.3–3.7) | 0.0004 |
| ALL | 45.1% (69/153) | 42.6% (90/211) | 1.1 (0.7–1.6) | 0.6426 |
| AML | 38.8% (38/98) | 38.8% (183/472) | 1.0 (0.6–1.5) | 0.9752 |
| MDS | 34.8% (11/32) | 38.0% (30/79) | 0.9 (0.4–2.0) | 0.7218 |
| NHL/HD | 28.0% (14/50) | 19.7% (158/803) | 1.6 (0.8–3.0) | 0.1546 |
| SAA/BMF | 25.3% (19/75) | 19.0% (11/58) | 1.4 (0.6–3.3) | 0.3835 |
| Other | | | | |
| PID | 37.3% (28/75) | – | ND | ND |
| NBL | 44.9% (44/98) | – | ND | ND |
| ES | 30.8% (8/26) | – | ND | ND |
| MM | – | 12.9% (169/1308) | ND | ND |
| Fungal infections | | | | |
| Total | 25.3% (163/650) | 6.3% (183/3200) | 5.5 (4.3–6.9) | < 0.0001 |
| Possible | 16.9% (98/650) | 2.3% (91/3200) | 6.1 (4.5–8.1) | < 0.0001 |
| Probable | 5.7% (42/650) | 2.1% (49/3200) | 4.4 (2.9–6.8) | < 0.0001 |
| Proven | 2.7% (31/650) | 1.6% (43/3200) | 3.7 (2.3–5.9) | < 0.0001 |
| Allo-HCT | 28.3% (142/499) | 14.0% (132/1070) | 2.8 (2.1–3.7) | < 0.0001 |
| Auto-HCT | 14.7% (21/151) | 2.5% (51/2135) | 6.6 (3.8–11.3) | < 0.0001 |
| ALL | 29.4% (45/153) | 11.3% (24/211) | 3.2 (1.8–5.6) | < 0.0001 |
| AML/MDS | 41.2% (47/114) | 13.2% (73/551) | 4.6 (2.9–7.2) | < 0.0001 |
| Viral infections | | | | |
| Auto-HCT | 6.6% (10/151) | 0.8% (17/2135) | 8.8 (4.0–19.6) | < 0.0001 |
| Allo-HCT | 56.3% (281/499) | 29.3% (314/1070) | 3.1 (2.5–3.8) | < 0.0001 |
| Multiple viral infections | 34.5% (97/281) | 27.1% (85/314) | 1.4 (1.0–2.0) | 0.0498 |
| Adenovirus (ADV) | 7.4% (37/499) | 2.9% (31/1070) | 3.5 (2.0–6.0) | < 0.0001 |
| Polyoma BKV (BKV) | 21.0% (104/499) | 5.2% (63/1070) | 5.2 (3.7–7.5) | < 0.0001 |
| Cytomegalovirus (CMV) | 28.9% (144/499) | 24.7% (264/1070) | 1.7 (1.3–2.1) | < 0.0001 |
| Epstein-Barr virus (EBV) | 19.4% (97/499) | 1.9% (20/1070) | 15.7 (9.2–26.1) | < 0.0001 |
| Influenza virus (INFL) | 2.2% (11/499) | 0.5% (5/1070) | 4.8 (1.6–13.9) | 0.0014 |
| Other | | | | |
| Varicella-zoster virus (VZV) | 1.8% (9) | 0.3% (3) | ND | ND |
| HHV6 | 1.2% (6) | 0.4% (4) | ND | ND |
| Respiratory syncytial virus (RSV) | 0.8% (4) | 0.2% (2) | ND | ND |
| Parainfluenza virus (PIF) | 0.4% (2) | 0 | ND | ND |
| Metapneumovirus (MPV) | 0.2% (1) | 0 | ND | ND |
| Rotavirus/norovirus | 8.4% (42) | 0.3% (3) | ND | ND |

Legend: *HCT*, hematopoietic stem cell transplantation; *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia; *MDS*, myelodysplastic syndromes; *NHL*, non-Hodgkin lymphoma (NHL); *HD*, Hodgkin lymphoma; *SAA*, severe aplastic anemia (SAA); *BMF*, bone marrow failure; *PID*, primary immunodeficiencies; *NBL*, neuroblastoma; *ES*, Ewing sarcoma; *MM*, multiple myeloma; *ND*, not done

patients, the risk was higher in children (HR = 1.7; $p < 0.001$), and in patients with late (> 21 days) hematological recovery (HR = 2.8; $p < 0.001$). In patients with multiple myeloma (MM), the risk was lower in comparison to all other patients (HR = 0.7; $p = 0.005$).

Outcome Overall outcome of bacterial infections was positive in 95.5% of infections in children and in 91.4% in adults (OR = 3.2; 95%CI = 1.6–6.5; $p = 0.0011$). The outcome of infections was better in children both after allo- and auto-HCT (Fig. 2a–c).

Table 3 Distribution and multidrug resistance (MDR) phenotypes of isolated Gram-negative species. The total number of MDR strains contains all types of resistance, including coexistence of mechanisms

| Pathogen | Children | | | | | Adults | | | | |
|---------------------------------------|----------|-------------|-------------|-----------|-------|--------|-------------|-------------|------------|------------|
| | Total | MDR | ESBL | AmpC | Other | Total | MDR | ESBL | AmpC | Other |
| Total | 233 | 158 (67.8%) | 153 (65.7%) | 5 (2.1%) | 4 | 843 | 404 (47.9%) | 378 (44.8%) | 70 (8.3%) | 41 (4.8%) |
| <i>Escherichia coli</i> | 58 | 44 (75.9%) | 44 (75.9%) | – | – | 242 | 75 (31.0%) | 75 (31.0%) | 7 (2.9%) | – |
| <i>Klebsiella pneumoniae</i> | 38 | 32 (84.2%) | 29 (76.3%) | – | – | 274 | 181 (66.1%) | 181 (66.1%) | 40 (14.6%) | 14 (5.1%) |
| <i>Enterobacter cloacae</i> | 56 | 52 (92.9%) | 52 (92.9%) | 3 (5.4%) | – | 115 | 79 (68.7%) | 70 (60.9%) | 21 (18.3%) | 10 (8.7%) |
| <i>Pseudomonas aeruginosa</i> | 22 | 1 (4.5%) | – | – | – | 74 | 36 (48.6%) | 22 (29.7%) | 2 (2.7%) | 14 (18.9%) |
| <i>Klebsiella oxytoca</i> | 13 | 12 (92.3%) | 12 (92.3%) | 1 (7.7%) | – | 17 | 7 (41.2%) | 7 (41.2%) | – | – |
| <i>Citrobacter freundii</i> | 8 | 4 (50.0%) | 3 (37.5%) | 1 (12.5%) | – | 7 | 5 (71.4%) | 5 (71.4%) | – | – |
| <i>Acinetobacter junii</i> | 1 | – | – | – | – | 19 | 4 (21.1%) | 4 (21.1%) | – | – |
| <i>Proteus mirabilis</i> | 2 | 2 (100%) | 2 (100%) | – | – | 19 | 4 (21.1%) | 4 (21.1%) | – | – |
| <i>Stenotrophomonas maltophilia</i> * | 11 | – | – | – | – | 29 | – | – | – | – |
| <i>Salmonella enteritidis</i> | – | – | – | – | – | 6 | – | – | – | – |
| <i>Enterobacter faecium</i> | 2 | – | – | – | – | 13 | – | – | – | – |
| <i>Enterobacter aerogenes</i> | 8 | 8 (100%) | 8 (100%) | – | – | 3 | 2 (66.7%) | 2 (66.7%) | – | – |
| <i>Klebsiella</i> spp. | 3 | 1 (33.3%) | 1 (33.3%) | – | – | – | – | – | – | – |
| <i>Morganella morganii</i> | 1 | 1 (100%) | 1 (100%) | – | – | 7 | 3 (42.9%) | 2 (28.6%) | – | 1 (14.3%) |
| <i>Enterobacter</i> spp. | 2 | – | – | – | – | 5 | 1 (20.0%) | 1 (20.0%) | – | – |
| <i>Serratia</i> spp. | – | – | – | – | – | 10 | 7 (70.0%) | 5 (50.0%) | – | 2 (20.0%) |
| Other species | 6 | – | – | – | – | – | – | – | – | – |

* *Stenotrophomonas maltophilia* is inherently resistant to most antibiotics except for cotrimoxazole (trimethoprim-sulfamethoxazole) and ticarcillin-clavulanate

Fungal infections

Incidence The 2-year incidence was 25.3% for children and 6.3% for adults ($p < 0.001$). It was higher both in children for allo-HCTs (28.3% vs 14.0%; $p < 0.0001$) and auto-HCTs (14.7% vs 2.5%; $p < 0.0001$) (Fig. 1d–f), regardless of the level of diagnosis: proven (2.7% vs 1.6%; $p < 0.0001$), probable (5.7% vs 2.1%; $p < 0.0001$), or possible IFD (16.9% vs 2.3%; $p < 0.0001$). At 2 years after HCT, incidences of proven/probable IFD were 8.4% and 3.7% ($p < 0.0001$) for children and adults, respectively (Fig. 1g–i). The frequency was higher both in pediatric patients with ALL (29.4% vs 11.3%; OR = 3.2, $p < 0.0001$) and AML/MDS (41.2% vs 13.2%; OR = 4.6, $p < 0.0001$), when compared to adults (Table 2). Additionally, two cases of PjP infections were diagnosed (one pediatric, one adult).

Identification of fungal species Total number of identified proven fungal infections was 74 (31 in children and 43 in adults), including 31 (42%) aspergilloses (*A. spp.* 6 vs 14; *A. fumigatus* 5 vs 2; *A. flavus* 2 vs 2), 34 (46%) candidiasis (*C. albicans* 9 vs 8; *C. glabrata* 3 vs 4; *C. krusei* 1 vs 1; *C. parapsilosis* 1 vs 0; *C. dubliniensis* 0 vs 1; *C. guilliermondii* 0 vs 1; *C. kefyr* 0 vs 1), 5 (6.8%) mucormycoses (*Mucor* spp. 1 vs 3; *Rhizopus* spp. 1 vs 0),

and 4 (5.2%) other species (*Fusarium* spp. 2 vs 1; *Cryptococcus* spp. 0 vs 1).

Timing Median time from day of HCT to IFD was 0.9 months (range 0–19) in children and 0.7 months (range 0–20) in adults. Median time of therapy of IFD was 24 days (range 1–590; quartiles 12–47) in children and 10 days (range 1–406; quartiles 9–26) in adults ($p < 0.0001$).

Risk factors In multivariate analysis, the risk of proven/probable IFD was higher after allo-HCT than auto-HCT (HR = 5.4; $p < 0.001$). In allo-HCT patients, the risk was higher in children than in adults (HR = 3.9; $p < 0.001$), in acute leukemia (HR = 3.8; $p < 0.001$), MUD vs MSD-HCT (HR = 1.5; $p = 0.013$), MMUD vs MSD-HCT (HR = 2.5; $p < 0.001$), late (> 21 days) hematological recovery (HR = 3.3; $p < 0.001$), acute GVHD before infection (HR = 1.5; $p = 0.021$), and chronic GVHD before infection (HR = 2.2; $p < 0.001$). In auto-HCT patients, the risk was higher in children than in adults (HR = 1.8; $p = 0.025$). Patients with MM were at lower risk of IFD in comparison to all other patients (HR = 0.6; $p = 0.005$) (Table 5).

Outcome Overall outcome of IFD was positive in 88.0% of infections in children and in 74.9% in adults (OR = 2.1;

Table 4 Distribution and multidrug resistance (MDR) phenotypes of isolated Gram-positive species. The total number of MDR strains contains all types of resistance, including coexistence of mechanisms

| Pathogen | Children | | | | | Adults | | | | |
|------------------------------------|----------|-------------|------------|------------|------------|--------|-------------|-------------|------------|------------|
| | Total | MDR | MRS | VRE | Other | Total | MDR | MRS | VRE | Other |
| Total | 287 | 125 (43.6%) | 56 (19.5%) | 49 (17.1%) | 34 (11.8%) | 461 | 185 (40.1%) | 111 (24.1%) | 59 (12.8%) | 15 (3.3%) |
| <i>Clostridium difficile</i> | 81 | – | – | – | – | 92 | – | – | – | – |
| <i>Staphylococcus epidermidis</i> | 51 | 36 (70.6%) | 36 (70.6%) | – | – | 129 | 74 (57.4%) | 74 (57.4%) | – | – |
| <i>Staphylococcus aureus</i> | 16 | 5 | 5 | – | – | 20 | 15 (75.0%) | 15 (75.0%) | – | – |
| <i>Staphylococcus hominis</i> | 9 | – | – | – | – | 25 | 4 (16.0%) | 4 (16.0%) | – | – |
| <i>Enterococcus faecium</i> | 86 | 69 (80.2%) | – | 49 (57.0%) | 34 (39.5%) | 53 | 41 (77.4%) | – | 26 (47.2%) | 15 (28.3%) |
| <i>Staphylococcus haemolyticus</i> | 18 | 5 (27.8%) | 5 (27.8%) | – | – | 33 | 10 (30.3%) | 10 (30.3%) | – | – |
| <i>Enterococcus faecalis</i> | 4 | – | – | – | – | 67 | 33 (49.3%) | – | 33 (49.3%) | – |
| <i>Staphylococcus spp.</i> | 2 | – | – | – | – | 19 | 8 (42.1%) | 8 (42.1%) | – | – |
| <i>Streptococcus mitis</i> | 1 | – | – | – | – | 6 | – | – | – | – |
| <i>Streptococcus spp.</i> | 3 | – | – | – | – | – | – | – | – | – |
| <i>Staphylococcus warneri</i> | 2 | – | – | – | – | – | – | – | – | – |
| <i>Corynebacterium spp.</i> | 1 | – | – | – | – | 7 | – | – | – | – |
| <i>Streptococcus pyogenes</i> | 2 | – | – | – | – | – | – | – | – | – |
| <i>Streptococcus pneumoniae</i> | 3 | – | – | – | – | 2 | – | – | – | – |
| <i>Streptococcus oralis</i> | 2 | – | – | – | – | 3 | – | – | – | – |
| <i>Micrococcus spp.</i> | – | – | – | – | – | 5 | – | – | – | – |
| Other species | 6 | – | – | – | – | – | – | – | – | – |

95%CI = 1.4–3.1; $p < 0.0001$). The outcome of IFD was better in children than adults both after allo- and auto-HCT, regardless of the level of IFD diagnosis: proven (88.6% vs 79.6%), probable (80.8% vs 66.2%), or possible (91.4% vs 78.6%) (Fig. 2d–j).

Viral infections

Incidence The 2-year incidence of viral infections was 56.3% for children and 29.3% for adults ($p < 0.0001$) after allo-HCT, and 6.6% vs 0.8% ($p < 0.0001$) after auto-HCT. The frequency was higher for CMV (28.9% vs 24.7%; OR = 1.7; $p < 0.05$), BKV (21.0% vs 5.9%; OR = 5.2; $p < 0.0001$), EBV (19.4% vs 1.9%; OR = 15.7; $p < 0.0001$), ADV (7.4% vs 2.9%; OR = 3.5; $p < 0.0001$), and influenza (2.2% vs 0.5%; OR = 4.8; $p = 0.0038$) (Table 2, Fig. 1j–l).

Viral infections after auto-HCT in children developed in 10 patients including 2 (1.3%) CMV, 1 (0.6%) influenza, 1 (0.6%) BKV, 1 (0.6%) ADV, and 5 (3.3%) rotavirus. Viral infections after auto-HCT in adults developed in 15 patients including 4 (0.18%) CMV, 5 (0.23%) influenza, 3 (0.14%) VZV, 2 (0.09%) HHV6, and 1 (0.04%) ADV.

Timing Median time from day of HCT to viral infection was 1.4 months (range 0–19) in children and 1.6 months (range 0–21) in adults. Median time of therapy of viral infection was

13 days (range 0–168; quartiles 6–24) in children and 12 days (range 0–401; quartiles 1–28) in adults.

Risk factors In multivariate analysis, the risk of infections was higher after allo-HCT (HR = 6.1; $p < 0.001$). In allo-HCT patients, the risk was higher in children (HR = 1.3; $p = 0.010$), in acute leukemia (HR = 1.7; $p < 0.001$), MUD vs MSD-HCT (HR = 2.0; $p < 0.001$), MMUD vs MSD-HCT (HR = 3.3; $p < 0.001$), MAC vs RIC (HR = 1.8; $p = 0.050$), acute GVHD before infection (HR = 1.5; $p < 0.001$), and chronic GVHD before infection (HR = 2.7; $p = 0.014$). Among auto-HCT patients, diagnosis of MM brought the lower risk of viral infections (HR = 0.5; $p < 0.001$) (Table 5).

Outcome Overall outcome of viral infections was positive in 98.6% of infections in children and in 92.3% in adults (OR = 3.3; 95%CI = 1.2–8.7; $p = 0.0096$). The outcome of viral infections varied between children vs adults: CMV (97.4% vs 94.1%; $p = 0.1$), BKV (99.0% vs 93.9%; $p = 0.075$), EBV (100% vs 81.3%; $p < 0.001$), ADV (100% vs 96.3%; $p = 0.3$), and influenza (100% vs 70%; $p = 0.5$) (Fig. 1k–o).

Deaths from infections

Frequencies Overall, 237 patients died from infection, including 7.8% (31/395) children and 18.4% (206/1120) adults

Table 5 Multivariate analysis of risk factors for infection

| Risk factor | Bacterial infection | | Fungal infection | | Viral infection | |
|-----------------------------------|---------------------|----------|------------------|----------|-----------------|----------|
| | HR (95%CI) | <i>p</i> | HR (95%CI) | <i>p</i> | HR (95%CI) | <i>p</i> |
| Allo vs auto | 2.9 (2.3–3.6) | <0.001 | 5.8 (4.6–6.9) | 0.021 | 16 (12–20) | <0.001 |
| Allo-HCT | | | | | | |
| Children vs adults | 2.1 (1.8–2.4) | <0.001 | 3.9 (3.3–4.5) | <0.001 | 1.3 (1.05–1.5) | 0.010 |
| Sex male vs female | 1.1 (0.9–1.3) | 0.065 | 0.9 (0.8–1.1) | 0.614 | 0.9 (0.8–1.1) | 0.180 |
| Acute leukemia vs other | 1.6 (1.4–1.8) | <0.001 | 3.8 (3.1–4.5) | <0.001 | 1.7 (1.4–2.1) | <0.001 |
| NHL/HD vs other | 1.2 (0.8–1.6) | 0.521 | 1.3 (0.8–1.8) | 0.358 | 1.4 (0.7–2.0) | 0.642 |
| Haplo vs other | 1.4 (0.8–1.9) | 0.162 | 1.3 (0.7–2.0) | 0.315 | 0.8 (0.3–1.3) | 0.520 |
| MUD vs MSD | 1.6 (1.2–2.1) | <0.001 | 1.5 (1.1–1.8) | 0.013 | 2.0 (1.3–2.7) | <0.001 |
| MMUD vs MSD | 2.0 (1.4–2.6) | <0.001 | 2.5 (2.1–2.9) | <0.001 | 3.3 (2.7–3.9) | <0.001 |
| BM vs PB | 1.4 (1.1–1.7) | 0.007 | 1.2 (0.8–1.7) | 0.382 | 0.8 (0.5–1.1) | 0.165 |
| MAC vs RIC | 1.3 (1.0–1.6) | 0.042 | 1.2 (0.9–1.6) | 0.068 | 1.8 (1.0–2.5) | 0.050 |
| TBI vs chemotherapy | 1.2 (1.0–1.4) | 0.055 | 1.3 (0.8–1.7) | 0.215 | 1.1 (0.7–1.5) | 0.386 |
| ANC recovery: >D21 vs ≤D21 days | 3.3 (2.6–4.1) | <0.001 | 1.2 (0.7–1.9) | 0.729 | 0.8 (0.5–1.1) | 0.065 |
| aGVHD before infection: yes vs no | 1.7 (1.4–2.1) | <0.001 | 1.5 (1.1–2.0) | 0.021 | 1.5 (1.1–2.0) | <0.001 |
| cGVHD before infection: yes vs no | 1.4 (1.1–1.6) | 0.014 | 2.2 (1.8–2.5) | <0.001 | 2.7 (2.3–3.1) | <0.001 |
| Auto-HCT | | | | | | |
| Children vs adults | 1.7 (1.3–2.1) | <0.001 | 1.8 (1.1–2.6) | 0.025 | 1.1 (0.6–1.7) | 0.872 |
| Sex male vs female | 1.2 (0.8–1.5) | 0.475 | 0.8 (0.3–1.5) | 0.235 | 0.8 (0.6–1.1) | 0.294 |
| Acute leukemia vs other | 1.8 (1.4–2.2) | <0.001 | 1.7 (1.2–2.1) | 0.004 | 1.5 (1.1–1.2.0) | 0.005 |
| NHL/HD vs other | 1.0 (0.80–1.2) | 0.922 | 0.9 (0.7–1.2) | 0.689 | 1.1 (0.7–1.4) | 0.745 |
| MM vs other | 0.7 (0.4–0.9) | 0.005 | 0.6 (0.3–0.8) | <0.001 | 0.5 (0.2–0.8) | <0.001 |
| ANC recovery: >D21 vs ≤D21 days | 2.8 (2.1–3.5) | <0.001 | 1.0 (0.5–1.5) | 0.936 | 0.9 (0.5–1.3) | 0.825 |

Legend: *HCT*, hematopoietic stem cell transplantation; *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia; *BM*, bone marrow; *PB*, peripheral blood; *TBI*, total body irradiation; *a/cGVHD*, acute/chronic graft versus host disease; *MUD*, matched unrelated donor; *MSD*, matched sibling donor; *MMUD*, mismatched unrelated donor; *MAC*, myeloablative conditioning; *RIC*, reduced intensity of conditioning; *NHL*, non-Hodgkin lymphoma (*NHL*); *HD*, Hodgkin lymphoma; *MM*, multiple myeloma; *ANC*, absolute neutrophil count; *D*, days

(OR = 0.4, 95%CI = 0.3–0.6; $p < 0.0001$). The distribution of deaths was different in children (35.5% bacterial, 48.4% fungal, 16.1% viral) than in adults (61.7% bacterial, 24.7% fungal, 13.6% viral).

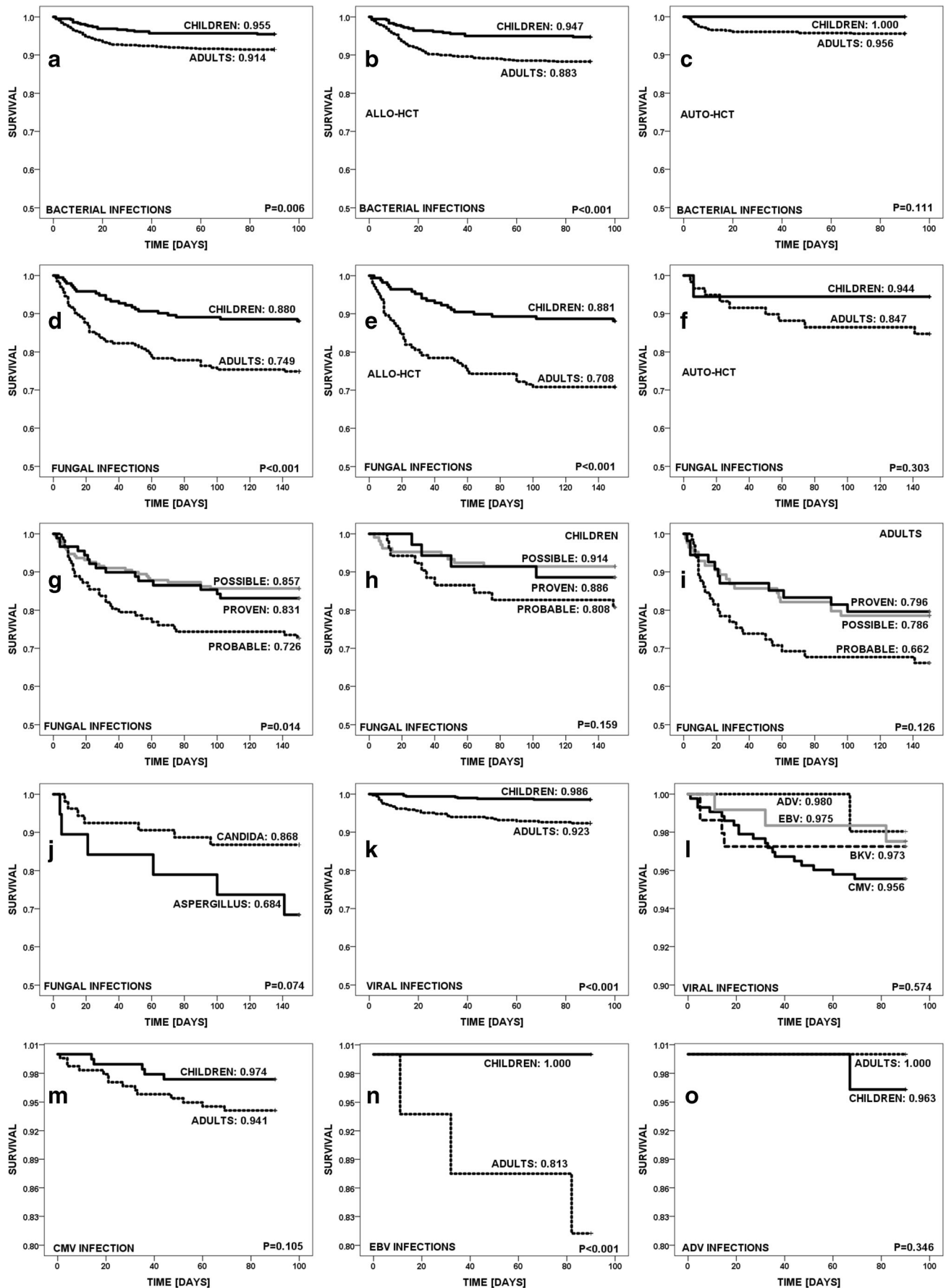
Risk factors for death from infectious complications In allo-HCT patients, in multivariate analysis, adults (HR = 3.3; $p < 0.001$), recipients of MMUD-HCT (HR = 3.8; $p < 0.001$), patients with acute leukemia (HR = 1.5; $p = 0.023$), chronic GVHD before infection (HR = 3.6; $p = 0.014$), CMV reactivation (HR = 1.4; $p = 0.038$), and in patients with duration of infection treatment > 21 days (HR = 1.4; $p = 0.038$) were associated with increased risk of IRM (Table 6). In separate analysis of patients with bacterial infections, the risk was higher in Gram-negative in comparison to Gram-positive infections (HR = 1.6; 95%CI = 1.1–2.1; $p = 0.031$).

Among auto-HCT patients, no child died of infection. Among adults, the risk of death was higher if duration of

treatment of infection was > 21 days (HR = 1.7; $p < 0.001$) (Table 6). In patients with MM, the risk was lower (HR = 0.4; $p < 0.001$). In separate analysis of patients with bacterial infections, there was a trend towards higher IRM in Gram-negative vs Gram-positive infections (HR = 1.8; 95%CI = 0.9–2.7; $p = 0.086$).

Discussion

In this study for the first time ever, simultaneous analysis and comparison of epidemiology and outcome of bacterial, fungal, and viral infections in a large cohorts of children and adults after HCT in a multicenter cross-sectional nationwide study were performed. Both groups largely differed in terms of distribution of primary diseases and their treatment, types of preparative regimens, and types of transplantation. Although both pediatric and adult transplant centers used generally very



◀ **Fig. 2** Outcome of infections. Bacterial infections **a** total, **b** allo-, and **c** auto-HCT. Fungal infections **d** total, **e** allo-, and **f** auto-HCT. With respect to level of IFD diagnosis **g** total, **h** children, and **i** adults. **j** Candida vs Aspergillus infections. Viral infections in **k** children vs adults. **l** CMV, BKV, EBV, and ADV infections. **m** CMV in children vs adults. **n** EBV in children vs adults. **o** ADV in children vs adults

similar strategy of anti-infective management [18], some differences between these settings existed, as pediatric centers used many off-label compounds. In this study, we analyzed patients over a period of 4 years, when anti-infective

prophylaxis and treatment did not change substantially in both pediatric and adult centers.

Bacterial infections occurred mainly during neutropenic, pre-engraftment phase. In adults, Gram-negative bacteria were more often documented, while in children Gram-positive species. The rate of MDR Gram-negative strains was higher in pediatric than in adult centers, while the rate of Gram-positive MDR was comparable in these cohorts. Our results indicate the shift of prevalence from Gram-positive to Gram-negative bacteria in a population of adult hematology patients and increasing incidence of MDR bacteria, especially Gram-

Table 6 Multivariate analysis for risk factors for death from infection after HCT

| Risk factor | HR (95%CI) | <i>p</i> |
|--|---------------|----------|
| Allo vs auto-HCT | 6.3 (5.2–7.6) | < 0.001 |
| ALLO-HCT | | |
| Adults vs children | 3.3 (3.0–3.6) | < 0.001 |
| Bacterial infection | 1.1 (0.8–1.4) | 0.527 |
| Fungal (<i>p/p</i>) infection | 1.6 (0.9–2.4) | 0.082 |
| Viral infection | 1.5 (0.7–2.2) | 0.392 |
| CMV reactivation | 1.4 (1.0–1.8) | 0.038 |
| Sex male vs female | 1.1 (0.9–1.3) | 0.962 |
| Acute leukemia vs other | 1.5 (1.1–1.9) | 0.023 |
| NHL/HD vs other | 1.0 (0.8–1.2) | 0.873 |
| Haplo vs other | 1.1 (0.8–1.3) | 0.285 |
| MUD/ vs MSD | 1.3 (0.8–1.8) | 0.259 |
| MMFD vs MSD | 3.8 (3.0–4.7) | < 0.001 |
| BM vs PB | 0.8 (0.3–1.4) | 0.337 |
| MAC vs RIC | 1.1 (0.5–1.7) | 0.872 |
| TBI vs chemotherapy | 1.1 (0.8–1.4) | 0.498 |
| aGVHD before infection: yes vs no | 1.0 (0.5–1.6) | 0.849 |
| cGVHD before infection: yes vs no | 3.6 (2.2–4.7) | < 0.001 |
| ANC recovery: >D21 vs ≤D21 days | 1.6 (0.8–2.5) | 0.115 |
| First infection: <D30 vs ≥D30 days | 1.1 (0.4–1.6) | 0.705 |
| Treatment duration of infection: >D21 vs ≤D21 days | 1.9 (1.1–2.7) | 0.027 |
| Auto-HCT | | |
| Adults vs children | 2.9 (1.5–4.8) | < 0.001 |
| Bacterial infection | 1.4 (0.7–2.2) | 0.585 |
| Fungal (<i>p/p</i>) infection | 1.4 (0.7–2.3) | 0.732 |
| Viral infection | 1.1 (0.2–1.9) | 0.856 |
| Sex male vs female | 1.3 (0.8–1.9) | 0.439 |
| NHL/HD vs other | 1.1 (0.3–1.9) | 0.823 |
| MM vs other | 0.4 (0.1–0.8) | < 0.001 |
| ANC recovery: >D21 vs ≤D21 days | 1.3 (0.9–1.8) | 0.092 |
| First infection: <D30 vs ≥D30 days | 1.1 (0.6–1.7) | 0.774 |
| Treatment duration of infection: >D21 vs ≤D21 days | 1.7 (1.2–2.5) | < 0.001 |

Legend. *HR*, hazard ratio; *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia; *AL*, acute leukemia; *HCT*, hematopoietic cell transplantation; *BM*, bone marrow; *PB*, peripheral blood; *CMV*, cytomegalovirus; *TBI*, total body irradiation; *a/cGVHD*, acute/chronic graft versus host disease; *MUD*, matched unrelated donor; *MSD*, matched sibling donor; *MMUD*, mismatched unrelated donor; *MAC*, myeloablative conditioning; *RIC*, reduced intensity of conditioning; *NHL*, non-Hodgkin lymphoma (NHL); *HD*, Hodgkin lymphoma; *MM*, multiple myeloma; *ANC*, absolute neutrophil count; *D*, days

negative [26, 27]. It is debatable, if use of quinolones in adults or oral gentamycin in children have possible negative impact in the selection of resistant gut microbiome [27]. We confirmed that irrespectively to age, transplant performed from alternative donor and prolonged neutropenia were independent risk factors for the development of bacterial infection [28]. The differences in bacterial epidemiology between children and adults resulted in differences in outcome of bacterial infections in these two cohorts, with a higher risk for death related to Gram-negative bacteria. High rate in bacterial infections was found for typical pediatric primary diagnoses like primary immunodeficiencies, neuroblastoma, and Ewing sarcoma; and opposite, in adulthood disease multiple myeloma, the rate was much lower and reached 12.9%.

Fungal infections were much more frequently diagnosed in children, regardless of the level of diagnosis; however, it was predominant for possible IFD. It reflects “real-life” pediatric strategy of reducing invasive diagnostics in children. It seems that lower incidence of IFD in adults might result from general strategy of protective environment in transplant setting and the prophylactic use of posaconazole during intensive chemotherapy in AML/MDS, according to ECIL recommendations [29–31]. Additionally, modified transplant procedure for pretransplant IFD, such as no-TBI conditioning, RIC, or use of PB as a stem cell source, could have possibly decrease the rate of fungal reactivations [1, 32]. Proven IFD were more often diagnosed in children. This was due mainly because of diagnosis of candidemia, as children usually have permanent, while adults rather temporarily central venous catheters. Most of children were also receiving TPN, while it was rather infrequent practice in adults. Relatively high rate of candidemia among proven IFD in children probably contributed to lower IRM than in case of invasive aspergillosis, as reported recently [33].

The incidence of viral infections was higher in children than in adults. This observation can be explained by immature immune system in children, resulting in primary infection or higher rate of reactivation of latent viruses. CMV and EBV were two most often diagnosed viruses in children after allo-HCT. CMV exerts direct and indirect effects in tissues and often plays a role of driver of another infections, including IFD, thus contributing to an increased post-transplant risk of life-threatening complications. With respect to respiratory viral infections, there is no current strategy of routine monitoring of community-acquired respiratory viruses; thus, no firm conclusion can be drawn on this topic from our study.

IRM was higher in adults, what has been evidence-proved for the first time. Additionally, IRM was higher in Gram-negative infections and in patients with acute leukemia. The outcome of infections was better in children both after allo- and auto-HCT. In addition to well-defined factors for mortality (acute leukemia, MMUD, GVHD, CMV reactivation),

duration of infection > 21 days was associated with an increased risk of death after infection.

The higher infection rate of MDI in children in comparison to adults can be explained by the following factors: (1) much higher rate of auto-HCT in adults resulting in overall lower incidence of infections in adults, especially seen in case of bacterial complications; (2) higher rate of patients with acute leukemia in pediatric cohort, with a well-known high incidence of infectious complications in acute leukemia [8, 34]; (3) much higher rate of diagnosis of possible IFD in children being the consequence of the positive results of imaging only; (4) higher incidence of viral infections in children, what can correspond to higher rate of primary infections; and finally, (5) real-life tendency of pediatricians to perform more detailed diagnostic procedures. Due to the same factors, the diagnosis of multiple myeloma was associated with a decreased risk for infection in multivariate analysis. On the other hand, the incidence of infectious complications in this group of patients was similar as presented in recent analyses [35–38].

The limitation of the study is its retrospective design; however, data were collected periodically. Also no routine screening was performed for viral infections except CMV and EBV. Thus, in most cases of viral infections, the diagnosis was bound to clinical symptoms.

In conclusion, the profile of infections and related deaths largely vary between children and adults. Our study proved age-dependent determinants of pediatric and adulthood profile of infectious complications after HCT: children have higher risk of all types of infections and a better outcome of bacterial infections, while in fungal and viral infections, the IRM was comparable between children and adults. Adult age, MMUD transplants, diagnosis of acute leukemia, chronic GVHD, CMV reactivation, and infection lasting > 21 days are relative risk factors for death from infection after HCT. The potential implication of this comprehensive analysis might be differential infection control and management strategies for children and adults.

Authorship contributions Study design: Jan Styczynski, Lidia Gil; Data analysis and interpretation: Jan Styczynski, Krzysztof Czyzewski, Przemysław Gałązka, Lidia Gil, Sebastian Giebel; Manuscript writing: Krzysztof Czyzewski, Jan Styczynski, Lidia Gil; Provision of important clinical data: All authors; Data check-up: Jan Styczynski, Krzysztof Czyzewski, Przemysław Gałązka, Lidia Gil; Statistical analysis: Krzysztof Czyzewski, Przemysław Gałązka, Jan Styczynski; Administrative support: Jan Styczynski, Lidia Gil; Critical revision of the manuscript: All authors; Final approval of manuscript: All authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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