

Antimicrobial prophylaxis in adults and children undergoing hematopoietic cell transplantation: 2021 Polish recommendations

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Abstract

Infections are still one of the most common causes of death after hematopoietic cell transplantation (HCT). Antimicrobial prophylaxis plays a crucial role in decreasing non-relapse mortality after HCT.

The objective of this guideline paper was the presentation of current recommendations of antimicrobial prophylaxis for children and adults after hematopoietic cell transplantation, prepared in cooperation with Polish scientific hematological societies. Recommendations were prepared by the working group and finally approved by all 23 Polish transplant centers for children and adults. Existing (European Conference on Infections in Leukemia (ECIL) and European Society of Blood and Marrow Transplantation (EBMT) guidelines, as well as the results of a survey performed among all Polish transplant centers, were the background material for the working group. Recommendations are presented in sections dedicated to antibacterial prophylaxis, antifungal prophylaxis, antiviral prophylaxis, as well as prophylaxis of toxoplasmosis and infections with *Pneumocystis jiroveci*. Recommendations on the principles of vaccination against COVID-19 are provided based on the state of knowledge in September 2021. A section on guidelines of environmental prophylaxis is also presented.

Key words: hematopoietic cell transplantation, children, adults, incidence, outcome, bacterial infections, viral infections, invasive fungal disease

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Introduction

Despite progress in the diagnostic field and the pharmacotherapy of infections, they are still one of the most common causes of death after hematopoietic cell transplantation (HCT). According to the latest analysis published by the European Society for Blood and Marrow Transplantation (EBMT), infections were responsible for about 22% of deaths, being the second commonest cause of death after autologous HCT (auto-HCT), and the third commonest cause after allogeneic HCT (allo-HCT) [1].

The post-HCT prophylaxis is adjusted to the risk of specific infections, which in turn depend mainly on the time elapsed after HCT. Traditionally, four phases with different frequencies of infectious categories are distinguished: the very early or pre-engraftment phase (up to 30 days post-HCT); the early post-engraftment phase (between days 30–100); the late post-engraftment phase (>100 days and up to one year); and the very late post-transplant phase (>1 year post-HCT). In the allo-HCT setting, prophylaxis also covers the risk of immunosuppression and graft-versus-host disease (GvHD).

Most infectious complications are reported in the very early and early periods post-HCT. However, in some patients, delayed immune reconstitution leads to a long-lasting vulnerability to certain infections. That is why appropriate antimicrobial prophylaxis remains one of the most critical aspects of post-transplantation care. In Europe, the major trends in this area are designed by the European Conference on Infections in Leukemia (ECIL), in nine editions 2005–2021 covering bacterial, fungal, viral and parasitic infections [2–16].

The objective of this guideline paper was to present current recommendations of antimicrobial prophylaxis in children and adults after hematopoietic cell transplantation, prepared in cooperation with Polish scientific hematological societies.

Material and methods

Experts in the field of infectious complications after HCT were invited to prepare recommendations on antimicrobial prophylaxis, both for children and adults, after HCT.

Table I. Grading system of recommendations

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

Recommendations were analyzed and approved by representatives of all transplant centers which had previously participated in a survey on practices of antimicrobial prophylaxis in Polish transplant centers [17, 18].

The presented guidelines are based on ECIL recommendations, adapted to Polish conditions, and supplemented by the results of the survey.

Recommendations are graded based on the modified system of recent ECIL meetings, taking into account the strength of the recommendation and the quality of evidence (Table I) [2, 3].

Prophylaxis of bacterial infections

Prophylaxis of bacterial infections in adults

The risk of infections in the pre-engraftment period should be individually assessed for each transplant patient, evaluating patient-, disease-, and treatment-related factors [19]. The level and duration of neutropenia, as well as mucosal damage, are the crucial risk factors of bacterial infections in the pre-engraftment phase. In the late post-transplant period, patients are at risk of infections caused by encapsulated bacteria (e.g. *Streptococcus pneumoniae* and *Haemophilus influenzae*) due to hypogammaglobulinemia and functional hyposplenism, resulting from GvHD and its treatment [20, 21].

Prophylaxis of bacterial infections in pre-engraftment period

Fluoroquinolone prophylaxis is recommended in transplant patients who are at high risk of bacterial infections due to expected profound and protracted neutropenia (defined as <100 neutrophils/mL for ≥ 7 days) (Table II) [19, 22, 23]. This refers mainly to allo-HCT with myeloablative conditioning (MAC). In patients treated with allo-HCT with non-myeloablative (NMA) protocols, or with auto-HCT, the risk of prolonged and profound neutropenia and, consequently, the risk of bacterial infections, is lower. In these settings, the

possible benefits of prevention should be weighed against its potential harm related to the negative influence of fluoroquinolones on the intestinal microbiome, increased risk of *Clostridium difficile* infection, and colonization/infection with fluoroquinolone-resistant or multidrug-resistant strains [22, 24]. Emerging data reporting an increasing frequency of fluoroquinolone-resistant gram-negative bacilli strongly indicates that the antibiotic policy of the transplant center should be adjusted in light of the local epidemiological data [24]. The implementation of an antimicrobial stewardship program is highly recommended in every center to promote optimal management of antibiotics [20, 22, 24].

Prophylaxis of bacterial infections in late post-transplant period (>100 days post-HCT)

Oral prophylaxis with penicillin is recommended during the immunosuppressive treatment for GvHD or hypogammaglobulinemia in areas with low pneumococcal resistance [20, 25]. Interchangeably, other agents, according to local antibiotic resistance patterns, might be used [20, 25]. An appropriate macrolide may be substituted depending on local practice [20, 25]. An applicable post-transplant vaccination schedule with Pneumococcal and *Haemophilus influenzae* vaccines plays a **crucial role** and should be performed in all HCT recipients [20, 25]. Supplementation with intravenous immunoglobulins (IVIG) is useful in patients with severe hypogammaglobulinemia (serum IgG level <4 g/L) with accompanying infections [20].

Prophylaxis of bacterial infections in children

Bacterial infections remain a significant challenge in HCT recipients, being an important cause of morbidity in these patients [26]. The incidence of these infections depends on various factors including underlying disease, the phase of treatment, MAC chemotherapy, immunosuppression induced by conditioning, and immunosuppressive effect of the prevention and/or treatment of GvHD [27]. Increasing

Table II. Recommendations for antibacterial prophylaxis in adults

Population	Recommendation	SoR/QoE
Pre-engraftment period (up to day 30 and beyond)		
Allo-HCT (MAC)	Fluoroquinolone prophylaxis	AII
Allo-HCT (NMA)	Fluoroquinolone prophylaxis	BIII
Auto-HCT	Fluoroquinolone prophylaxis	CII
Late post-transplant period (>100 days post-HCT)		
Allo-HCT (MAC, NMA)	Penicillin prophylaxis	BIII
	Macrolide prophylaxis	CIII
	Intravenous immunoglobulins (IVIG)	CIII
	Vaccination: <ul style="list-style-type: none"> • pneumococcal vaccine • <i>Haemophilus influenzae</i> vaccine 	BI BII
Auto-HCT	Penicillin prophylaxis if TBI used in conditioning	CIII
	Vaccination: <ul style="list-style-type: none"> • pneumococcal vaccine • <i>Haemophilus influenzae</i> vaccine 	BI BII

allo-HCT – allogeneic hematopoietic cell transplantation; MAC – myeloablative conditioning; NMA – non-myeloablative conditioning; auto-HCT – autologous hematopoietic cell transplantation; TBI – total body irradiation

antimicrobial resistance negatively affects prognosis and can influence eligibility for HCT. The high rate of bacterial infection in the peri-transplant period and the emergence of resistance to key antibiotic groups have led to widespread broad-spectrum antibiotic use [3]. Systemic antibacterial prophylaxis is one approach that can reduce the risk of bacterial infections, but carries the risk of drug toxicity or the emergence of antibiotic resistance.

We suggest that systemic antibacterial prophylaxis **should not be used routinely** for pediatric patients undergoing allo- or auto-HCT during pre-engraftment neutropenia or for those receiving systemic immunosuppression for the treatment of GvHD (DIII) (Table III). The evidence base that underlies this recommendation shows that antibacterial prophylaxis does not reduce mortality of HCT recipients, while it may have a certain impact on resistance in bacteremia isolates [28]. Besides the risk of increasing microbial resistance, antibiotics usually given in antibacterial prophylaxis are associated with negative consequences, i.e. musculoskeletal problems or central nervous system-related adverse events after fluoroquinolones and allergic reactions or gastrointestinal disorders after penicillin V [29]. Furthermore, as HCT recipients are routinely managed in a hospital during the high-risk period, there is an opportunity for very early empiric antibiotic administration and supportive care to reduce complications of bacteremia and severe sepsis [30].

Table III. Recommendations for antibacterial prophylaxis in children

Prophylaxis of bacterial infection in children	SoR/QoE
Recommendation: Routine antibacterial prophylaxis for pediatric patients undergoing HCT during pre-engraftment neutropenia is not recommended	DIII

As the recommendation is not supported by a randomized, controlled trial, a careful risk-benefit evaluation might favor antibacterial prophylaxis in particular patients.

It is important to emphasize that although routine antibacterial prophylaxis for HCT pediatric patients is not recommended, the implementation must always consider individual patient- and treatment-specific risk factors in deciding who merits antibacterial prophylaxis.

Prophylaxis of fungal infections

Prophylaxis of fungal infections in adults

In 2018, the European Conference on Infections in Leukemia (ECIL), the EBMT, the European Organization for Research and Treatment of Cancer, the Immunocompromised Host Society, and the European LeukemiaNet (ELN) published joint recommendations for antifungal prophylaxis [16].

These recommendations were adopted by national centers [31]. The choice of appropriate agent should be phase-specific, and adjusted to the risk of invasive fungal disease (IFD) and the local epidemiology of fungal infections, including construction works. For patients undergoing auto-HCT, routine prophylaxis is not recommended, although fluconazole 400 mg/day as prevention of *Candida* mucositis during the very early neutropenic phase may be considered (BIII) [32]. For allo-HCT, identified risk factors for mold IFD in the pre-engraftment/engraftment phases include active leukemia, cord blood transplantation (CBT), prior IFD, an alternative donor (AD) HCT recipient with iron overload or early/recurrent cytomegalovirus (CMV) infection or acute GvHD or delayed engraftment (≥ 3 -week neutropenia) or high-dose steroids for more than one week (≥ 2 mg/kg) [33]. The risk factors for the post-engraftment phase include acute GvHD grade III-IV, grade II after AD-HCT, acute GvHD non-responsive to steroids, acute GvHD receiving steroids, and age >40 years, subsequent acute and chronic GvHD, secondary neutropenia or recurrent CMV infection after AD-HCT [33, 34].

Antifungal prophylaxis in adults undergoing HCT: neutropenic phase (pre-engraftment)

In centers with mold IFD incidence $<5\%$, fluconazole is recommended (AI) when combined with mold-directed screening with biomarkers (galactomannan, GM) and/or high resolution computed tomography (HRCT), while an alternative approach should be used in centers with higher incidence (AIII). According to the latest update, mold-active

Table IV. Recommendations for primary antifungal prophylaxis in adults

Anti-fungal agent	Pre-engraftment		Post-engraftment
	Low risk of mold IFD	High risk of mold IFD	High-risk GvHD
Fluconazole p.o./i.v.	AI	DIII	DIII
Posaconazole (TDM) p.o.	BII	BII	AI
Voriconazole (TDM) p.o./i.v.	BI	BI	BI
Micafungin* i.v.	BI	CI	CII
Liposomal amphotericin B i.v.	CII	CII	CII
Aerosolized liposomal amphotericin B (plus fluconazole)	CIII	BII	No data

*No data for other echinocandins: anidulafungin and caspofungin; p.o. – per os; i.v. – intravenous; TDM – therapeutic drug monitoring (recommended)

azoles voriconazole 2 × 200 mg (BI) or posaconazole 3 × 200 mg (oral solution) or 1 × 300 mg (tablets) after a one-day loading dose of 2 × 300 mg (BII) should be used. Alternative options include micafungin 50 mg intravenous (i.v.) in low-risk (BI) and high-risk centers (CI) and liposomal amphotericin B IV (CII) [35]. Aerosolized liposomal amphotericin B in a dose of 10 mg twice weekly added to fluconazole 400 mg remains the option for high-risk centers (BII) [16].

Antifungal prophylaxis in adults undergoing HCT: post-engraftment phase

The experts contraindicate fluconazole in patients with GvHD and high-risk factors (AIII), while oral posaconazole continues to be the drug of choice (AI) [16, 36]. A low level of recommendations (CII) for micafungin and liposomal amphotericin B is based on limited data from randomized trials [16, 35]. The summarized recommendations are presented in Table IV.

The use of azoles poses the risk of drug-to-drug interactions in the HCT recipients, and Polish transplant centers avoid their use during the conditioning [17]. Centers should apply therapeutic drug monitoring (TDM) in the case of voriconazole (plasma target 1–6 mg/L) and posaconazole (plasma target >0.7 mg/L) [16]. Itraconazole, available in Poland in the form of capsules, has no recommendations for antifungal prophylaxis. Preliminary data supports isavuconazole's utility, but more trials are needed to determine its primary prevention role due to reported breakthrough IFD [37, 38].

Prophylaxis of fungal infections in children

Primary antifungal prophylaxis in children is strongly recommended irrespective of primary diagnosis during the neutropenic phase and until immune reconstitution, and in children with GvHD according to updated guidelines by ECIL-8 [2], and Polish recommendations, including dosing of antifungals [31]. Monitoring of *Aspergillus* using serum galactomannan (GM) levels is feasible, yet the negative predictive value is relatively high and other molds remain undetected. According to ECIL-8 guidelines, GM monitoring is valuable in children not receiving mold-active prophylaxis,

but experts discourage its use in those receiving mold-active prophylaxis due to false-negative results [2].

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

Primary antifungal prophylaxis is recommended in children undergoing allo-HCT in the neutropenic phase until engraftment (BII). Therapeutic options include fluconazole (effective only against selected yeasts), micafungin, posaconazole, or voriconazole. Due to possible drug-drug interactions, voriconazole should not be used during high-dose chemotherapy.

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

In the absence of GvHD, antifungal prophylaxis should be continued after engraftment until immune recovery. In the presence of GvHD treated with augmented immunosuppressive therapy, prophylaxis against mold and yeast infections is recommended (AIII). The available options include posaconazole (BI) and voriconazole (BI). Posaconazole oral suspension remains the treatment of choice (BI). Its twice-daily body-weight-based dosing algorithm has been proposed by Welzen et al. (Table V) [39]. Alternatively, for pediatric patients, from 1 month to 12 years of age, a starting dose of posaconazole 6 mg/kg three times daily may be used [40]. Parallel administration of proton pump inhibitors should be avoided during posaconazole prophylaxis. Posaconazole i.v. may be used alternatively for children with acute GVHD weighing >40 kg (300 mg daily i.v.). Posaconazole TDM will hopefully be shortly developed in Poland and offered to all transplant centers. A pilot study has been started in cooperation between Wrocław center and MonitLab in Poznań.

Antifungal prophylaxis in children undergoing auto-HCT

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

Table V. Posaconazole dosing algorithm in children

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

Antifungal prophylaxis in children with low risk for IFD development

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

Secondary antifungal prophylaxis

Secondary antifungal chemoprophylaxis is recommended, targeted against the previous fungal pathogen, for as long as the patient is neutropenic or under immunosuppression (AII). Either posaconazole or voriconazole may be considered (Table VI). Off-label isavuconazole may be used in very high-risk patients with previous fungal infections treated successfully with this agent.

Prophylaxis of viral infections

Prevention of CMV infection and disease

CMV infection has been associated with increased non-relapse mortality (NRM) in allo-HCT recipients [41]. Antiviral prophylaxis aims to prevent CMV replication in seropositive patients.

Universal prophylaxis leads to toxicities, detrimental for patients, including clinically significant myelosuppression associated with prolonged use of gancyclovir or valgancyclovir, which may also increase NRM. Moreover, high doses of acyclovir or valacyclovir reduced the risk of CMV infection, but not CMV disease, in randomized studies [42, 43].

Letermovir, a CMV-terminase inhibitor, significantly reduced CMV infection or reactivation and all-cause mortality at 24 weeks in CMV seropositive allo-HCT recipients, with no significant side effects [44]. Letermovir is active only against CMV, and therefore, acyclovir or valacyclovir is necessary to cover herpes simplex virus (HSV)/varicella zoster virus (VZV) prophylaxis. Patients who receive prophylaxis with letermovir should have CMV viremia monitored after drug discontinuation.

Currently, letermovir is the drug of choice for a universal CMV prophylaxis in CMV-seropositive allo-HCT recipients (Table VII). CMV infection and disease risk remains a concern among high-risk patients, including haploidentical HCT

Table VI. Recommendations for antifungal prophylaxis in children undergoing hematopoietic cell transplantation (HCT)

Drug	Allo-HCT, neutropenic phase	Allo-HCT, GvHD	Auto-HCT	Secondary prophylaxis
Posaconazole	+	++		+
Micafungin	+		+	
Fluconazole	+		+	
Voriconazole	+	+		+
Isavuconazole				(+)

allo-HCT – allogeneic hematopoietic cell transplantation; GvHD – graft-versus-host disease

Table VII. Recommendations for cytomegalovirus infection prophylaxis in allogeneic hematopoietic cell transplantation (allo-HCT) recipients [4]

Therapeutic agent	Adult patients	Pediatric patients
Letermovir 480 mg/day (240 mg/day, if cyclosporin is co-administered), starts on day of transplantation or up to 28 days afterwards, for 100 days after HCT	AI	–
Valacyclovir	BI	BI
Gancyclovir (2 × 5 mg/kg/day)	CI	CI
Valgancyclovir	CII	CII
Acyclovir	CI	CI
Foscarnet (180 mg/kg/day in 2–3 doses)	DII	CI
Intravenous immunoglobulin	DI	DI

(haplo-HCT), CBT, and T-cell-depleted (TCD) graft recipients. In this context, letermovir may be preferentially considered in this patient population.

Prevention of primary CMV infection

CMV-seronegative recipients should receive blood products from seronegative donors or leucocyte-depleted blood products, and the quality standard of less than 1×10^6 residual leukocytes per unit should be warranted (AI) [45, 46]. A CMV-seronegative donor should be chosen, when possible, for a CMV-seronegative recipient (AI), for haplo-HCT (AIII) [4]. In a MAC unrelated allo-HCT setting, for the CMV-seropositive recipient, a CMV-seropositive recipient should be chosen (BII). In haplo-HCT with post-transplant cyclophosphamide, a CMV-seropositive or seronegative donor is suitable (BII) [4].

Prevention of CMV infection and disease in children

In high risk pediatric patients including haplo-HCT, CBT and TCD graft recipients, several agents are recommended for CMV prophylaxis: valacyclovir (BI) [43, 47], gancyclovir (CI)

Table VIII. Recommendations for prevention of Epstein-Bárr virus (EBV)-post-transplant lymphoproliferative disorder (PTLD) and other EBV-related diseases [6]

Recommendation	Grading
Allo-HCT recipients and donors should be tested for EBV antibodies	AII
For EBV-seronegative recipients, an EBV-seronegative donor should be chosen	BII
For EBV-seropositive recipients, an EBV-seropositive donor might be preferred because of presence of EBV-CTL	CIII
Allo-HCT recipients at high risk for EBV-PTLD should be closely monitored for signs and symptoms related to PTLD	AII
After high-risk allo-HCT, prospective EBV-DNA-emia monitoring should be introduced	AII
For HLA-fully matched related, non-T-cell depleted graft recipients without GvHD, routine EBV-DNA-emia screening is not recommended	DII
For auto-HCT patients, routine monitoring for EBV-DNA-emia before and after HCT is not recommended	DIII

allo-HCT – allogeneic hematopoietic cell transplantation; CTL – cytotoxic T lymphocyte; HLA – human leukocyte antigen; GvHD – graft-versus-host disease

[48, 49], acyclovir (CI) [42], foscarnet (CI) [50] and valgancyclovir (CII). Data on letermovir use in children [51, 52] is insufficient to provide any recommendations for its use in a pediatric population. Due to a minor effect on prevention of CMV infection and disease, CMV-specific immunoglobulins and polyvalent IVIG are currently not recommended (DI) [53].

Prophylaxis of EBV-post-transplant lymphoproliferative disorder (PTLD) in adults and children

Active prevention is based on optimization of donor choice, conditioning regimen, and GvHD prevention (Table VIII). Data on Epstein-Bárr virus (EBV) prophylaxis in transplant settings is limited. Passive prophylaxis approaches, including a low dose of rituximab, unselected donor lymphocyte infusion (DLI), or EBV-specific cytotoxic T lymphocyte (EBV-CTL) infusion, can decrease the incidence of EBV-DNAemia. It should be noted, however, that the use of DLI for EBV-DNAemia or EBV-post-transplant lymphoproliferative disorder (PTLD) is not reported nowadays by transplant centers. Rituximab-based preemptive therapy can prevent the development of EBV-PTLD, benefiting recipients with higher loads of EBV-DNA. To date, there is no consensus as to when to initiate prophylactic or preemptive treatment. Current preemptive strategies for EBV-PTLD include reduction (RI) or withdrawal of immunosuppression therapy when feasible (AII) [54], rituximab (AII) [55, 56], and EBV-CTL (CIII) [57, 58]. Antiviral drugs are currently not recommended (DIII) [59] in the prophylaxis of EBV-reactivation (Table IX). RI is defined as a sustained decrease of at least 20% of the daily dose of immunosuppressive drugs [6].

Prophylaxis of HSV disease

Prophylaxis with an antiviral drug in herpes simplex virus (HSV)-seronegative allo-HCT recipients is not recommended (DIII) because primary HSV infections in this population are unusual. Due to the high rate of HSV reactivation in HSV-seropositive patients, prophylactic oral or IV acyclovir has been administered routinely in allo-HCT recipients,

Table IX. Preemptive treatment strategy for Epstein-Bárr virus (EBV)-post-transplant lymphoproliferative disorder (PTLD)

Therapeutic agent/strategy	Grading
Rituximab (B-cell depletion)	AII
Reduction or withdrawal of immunosuppressive therapy (RI)	AII
Adoptive transfer of EBV-CTL	CII
DLI	CIII
Antiviral agents	DII
IVig, interferon	DIII

CTL – cytotoxic T lymphocyte; DLI – donor lymphocyte infusion; IVig – intravenous immunoglobulin

Table X. Recommendations for herpes simplex virus (HSV) disease prophylaxis in HSV-seropositive adult patients [13, 60]

Therapeutic agent	Grading
Acyclovir from 3 × 200 mg to 2 × 800 mg/day p.o.	AI
Acyclovir 2 × 250 mg/m ² or 2 × 5 mg/kg i.v.	AI
Valacyclovir 2 × 500 mg/day p.o.	AII
Famcyclovir 2 × 500 mg/day	BIII

p.o. – per os; i.v. – intravenous

lasting 3–5 weeks after HCT (Table X). Allo-HCT recipients who develop GVHD or receive immunosuppressive treatment require prolonged HSV prophylaxis (BII). Intravenous acyclovir should be considered for patients with poor drug absorption or due to severe mucositis (CIII). Valacyclovir is an alternative prophylactic agent with good bioavailability, and famcyclovir may be considered as an alternative treatment [13, 60]. Famcyclovir is not yet available in Poland.

There are no specific recommendations for HSV prevention in a pediatric setting. In addition, there is no data on famcyclovir's safety and efficacy in children younger than 12 years. That is why a recommendation for this drug in a pediatric population cannot be given. However, according to the medical product characteristics, acyclovir dosing in children >2 years old is the same as for adults, while a half dose is recommended for children <2 years old.

Table XI. Recommendations for varicella zoster virus (VZV) disease prophylaxis for allogeneic hematopoietic cell transplantation (allo-HCT) recipients [13, 60]

Prophylaxis of VZV after allo-HCT	Grading
Acyclovir 2 × 800 mg/d p.o. (for children: 2 × 20 mg/kg) or valacyclovir once or twice daily: <ul style="list-style-type: none"> • for one year after allo-HCT or • in the presence of GvHD and immunosuppressive therapy beyond one year 	All BII
Prophylaxis after VZV exposure in VZV-seronegative patients	
Passive immunization with specific VZIG i.v. or i.m. (0.2–1 mL/kg) or normal IVIG (300–500 mg/kg) should be given immediately after exposure (<96 h), for patients who have chronic GvHD, or who are on immunosuppressive treatment, or who have undergone HCT within the last two years	All
Acyclovir 4 × 800 mg/daily (4 × 600 mg/m ² for children) or valacyclovir 3 × 1,000 mg/daily, (3 × 500 mg if body weight <40 kg), or famcyclovir 3 × 500 mg/daily; therapy should be administered from days 3–21 after exposure	AIII
If a second exposure occurs >21 days after a passive immunization or after the prophylaxis administration, a prophylaxis should be reintroduced	CIII
Seronegative HCT recipients should receive prophylaxis in case of exposure to a VZV vaccine having a varicella-like rash	BIII
Prophylaxis after VZV exposure for VZV-seropositive patients is optional	CIII

p.o. – per os; GvHD – graft-versus-host disease; VZIG – varicella-zoster immune globulin; i.v. – intravenous; i.m. – intramuscular; IVIg – intravenous immunoglobulin

Prophylaxis of VZV disease

The determination of VZV serostatus before transplantation should be done in all allo-HCT recipients (AIII). Acyclovir and valacyclovir prophylaxis were proven effective in several trials, and they are a primary preventive approach in the allo-HCT setting (Tables XI, XII). Prophylaxis in auto-HCT recipients is controversial [13]. Recommendations for adults and children are the same.

VZV-seronegative HCT recipients should not have contact with people with chickenpox or zoster (All) and vaccine recipients experiencing a rash after varicella vaccine (BIII). Vaccination of VZV-seronegative individuals who may be in contact with the patients during transplantation is a worthwhile preventive strategy, but should be performed at least four weeks before the start of conditioning (BIII). Zoster immune globulin (ZIG) and varicella-zoster immune globulin (VZIG) are passive antibody prophylaxis in seronegative recipients after exposure to varicella. If passive immunization is not available, acyclovir, valacyclovir, or famcyclovir as post-exposure prophylaxis are recommended.

Prophylaxis for BK Polyomavirus-associated hemorrhagic cystitis (BKV-HC)

No randomized controlled trial has yet been published to give a specific recommendation for the prevention of BKV-HC in adults and children. Anti-BKV prophylaxis is not available. Hyperhydration plus forced diuresis during conditioning regimen (BII) and/or bladder irrigation through a triple lumen Foley catheter are of limited value in a prophylactic setting (CII) [7, 61]. The risk of fluid overload for hyperhydration and the invasiveness of catheter positioning must be taken into consideration.

Fluoroquinolones (ciprofloxacin) are not effective for prophylaxis, and in fact increase the risk of antibiotic

Table XII. Administration of acyclovir in children

Indication	Dose
Prophylaxis HSV	2 × 5 mg/kg p.o.
Treatment of HSV mucositis	3 × 5 mg/kg i.v.; 10 days
Treatment of HSV visceral	3 × 10 mg/kg; 14–21 days
Prophylaxis VZV in IgG-seropositives	2 × 20 mg/kg (max. 2 × 800 mg)
Post-exposure prophylaxis VZV in IgG-seronegatives	2 × 20 mg/kg to 4 × 600 mg/m ² ; 21 days

p.o. – per os; HSV – herpes simplex virus; VZV – varicella zoster virus; IgG – immunoglobulin G

resistance (DII). Two studies showed a reduction of BKV replication in ciprofloxacin recipients, but without any impact on BKV-HC incidence [62, 63].

Prevention for HHV-6B infection (encephalitis)

Patients after CBT are at significant risk for both HHV-6 reactivation and HHV-6 encephalitis [64]. Routine testing of blood for HHV-6B in allo-HCT and testing donors or recipients for inherited chromosomally integrated HHV6 (CI-HHV-6) is not recommended due to a lack of recognized preemptive treatment thresholds, and the uncertain efficacy of preemptive therapy (DII). HHV-6 PCR results must be interpreted with caution due to the possibility of CI-HHV-6 in the recipient or allografted cells. In patients with CI-HHV-6, latent HHV-6 DNA will be detected by PCR test in all clinical samples. However, this may not reveal viral replication, and antivirals will not reduce the viral load (in whole blood samples, HHV-6 viral loads are typically >10⁶ copies/mL). Encephalitis is the only well recognized HHV-6 disease in allo-HCT recipients; other clinical manifestations are less

Table XIII. Recommendations for adenovirus disease prophylaxis for allogeneic hematopoietic cell transplantation recipients [14]

Recommendation	Grading
Prophylaxis with an antiviral drug is not recommended	BIII
In patients with viremia and at least one risk factor, preemptive therapy with cidofovir (3–5 mg/kg/week for 2–3 weeks, followed by 3–5 mg/kg every other week or 1 mg/kg, three times a week)	BII

established. There is insufficient evidence to recommend the routine use of antiviral prophylaxis or preemptive therapy for HHV-6 infection in adults and children (DII) [5].

Prophylaxis of adenovirus (ADV) infection

ADV infection is diagnosed mainly in the 2–3 months after allo-HCT. Although some patients are asymptomatic and eliminate the virus spontaneously, a quick increase of viral load to multi-organ disease with organ insufficiency is possible. Nevertheless, prophylaxis with any antiviral drug is not recommended for adults and children (BIII) (Table XIII). Cidofovir is recommended for preemptive antiviral treatment in allo-HCT patients with viremia and at least one risk factor both for children (allo-HCT with *in vivo* or *ex vivo* T-cell depletion; allo-HCT with unrelated donor graft; allo-HCT with unrelated cord blood graft; grade III–IV graft-versus-host disease; and severe lymphopenia with <200 cells/ μ L PB) and for adults (allo-HCT with haploidentical donor or unrelated cord blood graft; grade III–IV GvHD; severe lymphopenia with <200 cells/ μ L PB; and treatment with alemtuzumab) (BII) [14].

Prevention of community-acquired respiratory virus infection (CARV) in adults and children

Good personal hygiene (i.e. frequent hand washing, covering mouth when coughing and sneezing, safe disposal of nasal and oral secretions) is strongly recommended for allo-HCT patients and their contact persons (All) (Table XIV). Patients undergoing HCT should avoid people with respiratory tract infections in the hospital and the community (All). Young children should not be allowed to visit patients and wards because of the greater risk of CARV transmission with prolonged shedding (BII). Entering HCT wards and seeing HCT patients should be restricted for healthcare workers and visitors with respiratory tract infections (All). In HCT patients with respiratory tract infection inside care facilities, infection control measures should be incorporated, including isolation rooms and protective equipment (coat, gloves, masks, eye protection) for staff and visitors (All). Outpatients with respiratory tract infections should be placed in rooms separated from other HCT patients

Table XIV. Recommendations on prevention of community-acquired respiratory virus (CARV) for allogeneic hematopoietic cell transplantation (allo-HCT) recipients [12]

Recommendation	Grading
Good personal hygiene (frequent hand washing, covering mouth when coughing and sneezing, safe disposal of nasal and oral secretions) is strongly recommended for allo-HCT patients and contact persons	All
HCT patients should avoid contact with people with respiratory tract infections in the hospital and the community	All
Young children should not be allowed to visit patients and wards because of the greater risk of CARV exposure, prolonged shedding, and transmission	BII
Healthcare workers and visitors with respiratory tract infections should be prevented from visiting HCT patients and wards	All
In HCT patients with respiratory tract infection inside care facilities, infection control measures should be used, including isolation rooms and protective equipment to support staff and visitors (coat, gloves, masks, eye protection)	All
Outpatients with respiratory tract infections should be admitted and treated in rooms separated from other HCT patients and the HCT ward	All
In pediatric HCT recipients aged <2 years, palivizumab may be considered during RSV outbreaks in the community, indicating an increased exposure	CIII
In HCT recipients with hypogammaglobulinemia (<4 g/L), IVIg may reduce the risk of morbidity and mortality secondary to respiratory tract infections caused by CARV	CIII

IVIg – intravenous immunoglobulin

and an HCT ward (All). In pediatric HCT recipients aged <2 years, palivizumab, an intravenous monoclonal antibody specific for respiratory syncytial virus (RSV), may be considered during RSV outbreaks in the community (CIII). In HCT recipients with hypogammaglobulinemia (<4 g/L), IVIg may reduce the risk of morbidity and mortality secondary to respiratory tract infections caused by CARV (CIII) [12].

Prophylaxis of influenza in adults and children

To avoid transmission of influenza, patients and healthcare staff should apply the same general precautions for preventing CARV infection.

Vaccination with seasonal inactivated influenza vaccine is recommended yearly in all HCT recipients older than 6 months (All) (Table XV). The vaccine is given at least three months after HCT, and preferably prior to the flu season (BIII). Due to the risk of suboptimal immunity in case

Table XV. Recommendations on prevention of influenza for hematopoietic cell transplantation (HCT) recipients [15]

Prevention of influenza with vaccination	Grading
Vaccination with seasonal inactivated influenza vaccine is recommended in all HCT recipients older than 6 months	All
The vaccine should be given at least three months after HCT, preferably prior to the influenza season	BIII
Post-exposure antiviral prophylaxis	
Oseltamivir for at least 10 days	CIII

of vaccination performed <6 months post-HCT, a second dose of vaccine can be considered [60]. After exposure to a confirmed or probable case of flu, antiviral prophylaxis with oseltamivir for at least 10 days is recommended in HCT recipients who are less than 12 months after HCT, or later if immunocompromised (CIII) [15].

Prophylaxis of SARS-CoV-2/COVID-19 in adults and children

A new coronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – appeared at the end of 2019, and caused a disease called COVID-19. The WHO classified COVID-19 as a pandemic on 11 March 2020 [65]. Mortality among HCT patients caused by this disease was over 22% in adults and 7% in children [66].

There is no specific antiviral agent active against SARS-CoV-2. Thus, non-specific preventive measures typical for CARV infections are mandatory. A number of new-generation vaccines are available nowadays. We recommend following EBMT guidelines: HCT patients should be vaccinated with whatever vaccine is available but not live-attenuated vaccine or vaccine containing replicating viral vectors [67]. Vaccination against COVID-19 should take priority over the regular vaccinations program; the vaccine should routinely be administered alone. The vaccination program should be initiated at least three months after HCT; although if the transmission rate is low, it is advised to wait six months after HCT to initiate vaccination. Controlled GvHD is not a contraindication for vaccination [67]. It will be necessary to administer additional or periodic shots. As of September 2021, children over 12 years should be vaccinated. As of December 2021, children over 5 years should be vaccinated (note added at proof).

Prophylaxis for toxoplasmosis

Toxoplasmosis is a life-threatening condition with an incidence depending on seroprevalence in the population. Toxoplasmosis is seen mainly after allo-HCT, but cases after auto-HCT have been published. The disease occurs mainly as reactivation in previously infected individuals, however primary infection or re-infection after transplant can be also

observed. The main risk factors for its development include patient seropositivity, allo-HCT and GVHD.

Recommendations on prevention of toxoplasmosis [68]:

1. In all patients and their donors, serostatus should be determined prior to transplant.
2. Avoiding eating uncooked meat of any type or drinking contaminated water should be recommended to all patients before and after transplant.
3. Primary chemoprophylaxis should be offered to seronegative recipients transplanted from a seropositive donor.
4. Secondary chemoprophylaxis is recommended to all seropositive recipients, regardless of donor serostatus.
5. Chemoprophylaxis is based on TMP/SMX taken at least three times per week for ≥ 6 months:
 - a) 80/400 mg daily,
 - b) 160/800 mg, three days per week.
6. Alternative chemoprophylaxis includes:
 - a) Pyrimethamine and sulfadoxine (fancidar): 2–3 tablets per week,
 - b) Atovaquone: 1,500 mg daily,
 - c) Dapsone: 100 mg daily.
7. Weekly qPCR monitoring is advocated when prophylaxis is not being used, is used for less than six months, or when the dose or type of prophylactic medicines are not adequate (i.e. pentamidine).

Prophylaxis for *Pneumocystis jiroveci*

Pneumocystis jiroveci (PjP, previously known as PcP) causes life-threatening pneumonia in immunocompromised patients. According to ECIL guidance, primary prophylaxis should be offered to all recipients after allo-HCT.

The drug of choice is TMP/SMX (trimethoprim/sulfamethoxazole) in a dose of 80/400 mg daily or 160/800 mg, three times weekly from engraftment for at least six months or longer where immunosuppression is ongoing. Second-line alternatives include: pentamidine aerosolized (300 mg per month) or IV, or atovaquone (1,500 mg per day), or dapsone (2 × 50 mg, daily) [8].

Environmental prophylaxis

Global recommendations on protective environment in the HCT setting have been prepared internationally (Table XVI) [69] but adopted locally [18, 70]. Additionally, general precautions for patients and healthcare staff to prevent CARV infection should always be implemented in everyday clinical practice.

Discussion

Antimicrobial prophylaxis plays a crucial role in lessening NRM after HCT [71]. These joint recommendations summarize the most important aspects based on available data to

Table XVI. Global Recommendations on Protective Environment

Global Recommendations on Protective Environment (GRPE)	Grading
1. Ventilation: ≥ 12 air changes per hour	AIII
2. Central or point-of-use HEPA filters with 99.97% efficiency for removing particles $\leq 0.3 \mu\text{m}$ in diameter	AIII
3. Filters should be replaced regularly based on manufacturers' recommendations, and, when there is ongoing construction, filtration efficiency should be monitored frequently to best determine appropriate time for replacement	AIII
4. Directed airflow so that air intake occurs at one side of room and air exhaust occurs at opposite side	BIII
5. Consistent positive air pressure differential between patient's room and hallway $\geq 2.5 \text{ Pa}$	BIII
6. Well-sealed rooms (e.g. filling gaps between walls and windows, outlets, floor, and ceiling) should always be used for HCT patients to prevent infiltration of air from outside room that could allow entry of spores and hinder maintenance of proper pressure differential	BIII
7. Continuous pressure monitoring, especially while rooms are occupied	BIII
8. Self-closing doors to maintain constant pressure differentials	BIII
9. Monitoring systems that will set off an alarm when pressure differential between any protective environment room and adjacent hallway or anteroom falls $< 2.5 \text{ Pa}$, to alert staff to possible engineering failures	CIII
10. To enable nursing staff to observe HCT recipient even when doors are closed, windows can be installed in either door or wall of HCT recipient's room	CIII

help transplant physicians in their everyday practice. We have tried to adjust these recommendations to a local market. However, we also included new antimicrobial agents like letermovir and isavuconazole.

Although limited refunding options severely hinder access to them in Poland, we believe that this situation will change in the near future. The market of azoles differs from that of other European countries. That is why itraconazole in oral suspension was not mentioned, while we listed posaconazole in tablets, as this form may soon become available in Poland. Although, according to the current ECIL or EBMT guidelines, isavuconazole is nowadays not listed in recommendations for prophylactic treatment, we provided this possibility both for children and adults. This is due to the increasing number of new publications regarding its off-label use in antifungal prophylaxis in a population of patients with hematological malignancies and patients undergoing allogeneic transplantation. There are several advantages of

this drug compared to other antifungal azoles: less drug interactions, less hepatic toxicity, and less renal impairment.

Antibacterial prophylaxis remains an unsolved issue due to the side effects of fluoroquinolones, unfavorable influence on gut microbiota, and increased bacterial resistance to this group of antibiotics. Transplant centers follow different strategies: continue this type of prophylaxis, or abandon pharmacological prevention with increased attention to neutropenic fever, or replace fluoroquinolones with another agent. Randomized prospective studies should be designed to determine which attitude is the optimal solution for HCT patients.

Moreover, there is an urgent need to implement and standardize TDM of voriconazole and posaconazole in our laboratories. This would increase the safety and efficacy of antifungal management.

Regarding CARV, we have given general recommendations with no stress on the current SARS-CoV-2 pandemic since most preventive precautions are common while the therapeutic approach is very dynamic and systematically updated by the EBMT.

Due to constant development in the field of HCT and new evidence regarding antimicrobial prophylaxis and treatment being published constantly, regular updates of these recommendations will be required.

Authors' contributions

Design of study: JS, LG. Analysis of recommendations and final approval: all authors. The following authors wrote primary versions of respective sections: AP (Introduction, Antifungal prophylaxis in adults, Discussion); KK (Antifungal prophylaxis in children); AF (Antibacterial prophylaxis in adults); OZS (Antibacterial prophylaxis in children); BPJ (Antiviral prophylaxis in adults); KC (Antiviral prophylaxis in children); LG (Prophylaxis of toxoplasmosis and infections with PjP); JS (Introduction, Methods, COVID-19 prophylaxis, Environmental prophylaxis, Discussion).

Conflicts of interest

JS – lecture fees or participant in meetings supported by Pfizer, MSD, Gilead, TEVA, and Astellas. KC – lecture fees or participant in meetings supported by MSD and Gilead. KK – lecture fees or participant in meetings supported by Pfizer, MSD, and Gilead. BB – lecture fees or participant in meetings supported by Amgen, and Celgene/BMS. All other authors declared no conflict of interest.

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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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