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Evaluation of colonization and infection profile in allogeneic hematopoietic stem cell transplantation recipients

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Abstract

Introduction: Infections are one of the main causes of death after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Material and methods: We conducted a single-center retrospective analysis of colonization and infection epidemiology in 44 patients who underwent matched related donor (MRD) allo-HSCT between 2012 and 2022.

Results: Colonization was observed in 84.1% of patients before allo-HSCT. The most common location was the anus, colonized in 55.4% of patients, mostly by *Klebsiella pneumoniae* ESBL(+) — 28.6%. Multi-drug resistant bacteria (MDR) accounted for 50.7% of positive colonization cultures before allo-HSCT.

In the post-transplantation period (i.e. up to 100 days after allo-HSCT), infections occurred in 86.4% of patients. Bacteremia was observed in 47.7% of patients, mostly caused by methicillin-resistant coagulase-negative *Staphylococcus epidermidis* — 39.4%. Infection of the skin and soft tissue near the central line was found in 27.3% of patients, urinary tract infections in 56.8%, and gastrointestinal infections in 38.6%. Fungal infections were reported in 31.8%. MDR pathogens accounted for 58.1% of all infecting pathogens. The most common resistance was extended-spectrum beta-lactamase (ESBL), accounting for 50.8% of all MDR strains. Viral reactivations were detected in 29.5% of patients.

59.5% of colonized patients developed an infection with the pathogen responsible for their previous colonization. Infections with such pathogens were significantly more frequent in colonized patients than with *de novo* pathogens ($p = 0.04$).

Conclusions: The results of the presented study highlight the role of colonization assessment as a tool to identify patients at high risk of developing post-transplant infections, guiding the possibility of efficient targeted antibiotic therapy.

Keywords: hematopoietic stem cell transplantation, infections, bacteremia

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Introduction

A key action of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the ability to replace the recipient's abnormal immune and hematopoietic cells with long-term repopulation of cells from a healthy donor. In 2021, the European Society for Blood and Marrow Transplantation (EBMT) reported c.47, 400 HSCTs [1].

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Allo-HSCT was performed in 19,806 of these patients (42%) and its main indications were myeloid malignancies (58%), lymphoid malignancies (28%), and non-malignant disorders (13%) [1].

Allo-HSCT is still associated with a high risk of treatment-related mortality (TRM), which is mainly caused by infection, toxicity, and graft-versus-host disease (GvHD) [2]. However, according to the Center for International Blood and Marrow Transplant Research (CIBMTR), the 100-day TRM in acute myeloid leukemia (AML) patients transplanted using myeloablative conditioning (MAC) regimens decreased from 15% to 6% in matched related donors (MRD), and from 37% to 14% in matched unrelated donors (MUD) [3]. Furthermore, several studies have reported a significant decrease in TRM over time, which is explained as being the result of less toxic conditioning, more accurate HLA matching, advances in the prevention and treatment of GvHD, and more effective infection prophylaxis and treatment [4].

Nevertheless, infection-related mortality (IRM) remains a major challenge associated with the HSCT procedure, particularly when using alternative donors. The emergence of multidrug-resistant pathogens has become a global threat connected with life-threatening opportunistic infections causing an increased risk of both early and late IRM [5]. The CIBMTR estimates that in MRD, HSCTs infections are responsible for 19% and 17% of deaths in the early and late post-transplantation periods, respectively, whereas in haploidentical HSCTs, IRM is 28% and 17%, respectively. In MUD, HSCT infections account for 22% of early deaths, and 16% of late ones [6].

More than half of IRM is associated with an unspecified etiology. Of the known factors, IRM of bacterial origin accounts for c.35%, fungal — 25–30%, viral — 20–30%, parasitic — 3–5%, and infections of mixed origin — 12% [5].

The most important predictors determining the occurrence of infections after allo-HSCT are the patient's pre-transplant colonization, and the microbial epidemiology of the transplant center. In addition, other factors are also crucial for infection development such as the severity of treatment-induced neutropenia (<7 vs. >7 days, absolute neutrophil count (ANC) <0.5 G/L duration), older age, mucositis associated with chemotherapy toxicity, donor-recipient virological status (CMV, EBV), the type of cancer, the type of conditioning (myeloablative vs. non-myeloablative), the type of donor (i.e. related, unrelated, alternative) as well as the occurrence of GvHD [2, 7–9].

Material and methods

We performed a retrospective, single-center analysis to assess the colonization with pathogenic microorganisms and the profile of its changes after MRD HSCT. In addition, we analyzed the incidence of infections up to 100 days after MRD allo-HSCT, and the effectiveness of the prophylaxis used.

Table I. Allogeneic hematopoietic stem cell transplantation indications

Diagnosis	N [%]	Conditioning regimen in a particular diagnosis	N [%]
AML	23 (52.3)	Flu/Bu 4	8 (34.8)
		BuCy 2	7 (30.4)
		TBI/Cy	3 (13.1)
		Flu/Bu 2	2 (8.8)
		Flu/Bu 4 + ATG	1 (4.3)
		Flu/Bu 2 + ATG	1 (4.3)
		Cy/ATG	1 (4.3)
ALL	8 (18.1)	TBI/Cy + ATG	5 (62.5)
		BuCy 2	2 (25)
		Cy/ATG	1 (12.5)
AA	4 (9.1)	Cy/ATG	4 (100)
MDS	2 (4.5)	Treo/Flu/ATG	1 (50)
		Treo/Cy	1 (50)
T-PLL	2 (4.5)	Flu/Bu 4	2 (100)
CML	1 (2.3)	Flu/Bu 4	1 (100)
aCML	1 (2.3)	Flu/Bu 4	1 (100)
HL	1 (2.3)	Flu/Bu 2	1 (100)
MPAL	1 (2.3)	BuCy 2	1 (100)
T-LBL	1 (2.3)	TBI/Cy	1 (100)

AML — acute myeloid leukemia; ALL — acute lymphoblastic leukemia; AA — aplastic anemia; MDS — myelodysplastic syndrome; T-PLL — T-cell prolymphocytic leukemia; CML — chronic myeloid leukemia; aCML — atypical chronic myeloid leukemia; HL — Hodgkin lymphoma; MPAL — mixed phenotype acute leukemia; T-LBL — T-cell lymphoblastic lymphoma; Bu — busulfan; Cy — cyclophosphamide; Flu — fludarabine; TBI — total body irradiation; ATG — anti-thymocyte globulin

All 44 patients, 17 of whom were men (39%), and 27 women (61%), with a median age of 45 years (range: 18–68) underwent allo-HSCT transplantation between January 2012 and December 2022 in the Department of Hematology of the Medical University of Lodz, Poland. Indications for allo-HSCT procedure are set out in Table I. Allo-HSCT was performed in accordance with current EBMT recommendations [10].

A central vascular catheter was implanted in all patients before the chemotherapy prior to the transplantation procedure. Microbiological cultures of urine and material collected in the form of swabs from the throat, nasal cavity, and anal area were performed on each patient in the pre-transplant period, and additionally at weekly intervals after the allo-HSCT procedure. The results of these tests were used to determine the colonization. Each patient gave informed consent for access to his or her clinical data. This study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

According to the guidelines of the European Conference on Infections in Leukemia (ECIL) and the EBMT, prophylactic antibacterial treatment (ciprofloxacin) was administered to all patients from the start of chemotherapy until ANC >0.5 G/L was reached. Antiviral (acyclovir), antifungal (fluconazole), and pneumocystosis (cotrimoxazole) prophylaxis was administered until six months after allo-HSCT, or until the end of immunosuppression if this was a longer period.

Moreover, environmental prophylaxis was administered to all patients, which was associated with increased restriction of aseptic and antiseptic regimens in the Marrow Transplant Unit. This prophylaxis included the use of air-conditioned isolation rooms with high-efficiency particulate arresting (HEPA) air, no contact with visitors, an appropriate diet with thermal treatment and strict personal hygiene, and sterilization of clothes and bedsheets. The median duration of hospitalization for patients undergoing allo-HSCT at our center was 47 days (range 31–74).

Bacteremia was defined as a positive microbiological culture from a single or, in the case of gram-positive infections, two consecutive, blood cultures taken from a febrile patient.

In a case of fever in patients with no clinically overt sign of infection, nopathogen colonization nor any prior infection with a resistant pathogen, one of two empiric treatment options was used: a cephalosporin with activity against *Pseudomonas* (cefepime or ceftazidime) or piperacillin with tazobactam. For patients with a complicated clinical course of infection, carbapenem was administered in combination with a glycopeptide/oxazolidine or a beta-lactam antibiotic with activity against *Pseudomonas* along with an aminoglycoside in combination with a glycopeptide/oxazolidine. If the patient was not colonized, carbapenem was administered along with an aminoglycoside and glycopeptide/oxazolidine [11].

The presence of colonization with a resistant pathogen was the reason for implementing targeted antibiotic therapy. Recommendations were modified according to the results of microbiological cultures and imaging studies, and treatment was continued for at least 72 hours after the fever and other signs of infection had resolved, and until the presence of ANC >0.5 G/L for two consecutive days. However, in patients with fever >72–96 hours despite the introduction of broad-spectrum antibiotic therapy, empirical antifungal therapy with an amphotericin B lipid complex or caspofungin was used [11].

Statistical analysis was performed using multivariate tables and the Chi^2 test with Yates's correction to compare qualitative parameters. For quantitative variables, such as the number of days of hospitalization, fever, and antibiotic therapy, we performed a normality check of the distribution using the Shapiro–Wilk test. For comparisons of variables without a normal distribution, we used the Mann–Whitney U test with correction for continuity and the Kruskal–Wallis test for comparisons of more than two groups. We looked for differences between groups using post-hoc tests. We assessed patient survival through the Kaplan–Meier method and compared using the log-rank test. We created univariate and multivariate survival analysis models using the Cox proportional hazards method. In all analyses, we used P-values with a significance level of 0.05. In the survival analysis, the confidence interval was 95%.

Results

Analysis of patients who underwent MRD allo-HSCT

Evaluation of colonization in pre-transplant period

Colonization with any pathogen before allo-HSCT was found in 84.1% (37/44) of patients, and in 54.5% (24/44) of them the place undergoing colonization analysis was colonized by more than one pathogen. The total number of sites colonized by at least one pathogen was 56. The anal region was most frequently colonized by at least one pathogen [55.4% (31/56) of all colonized sites], followed by the urinary tract 30.3% (17/56), nasal cavity 8.9% (5/56), and then the throat 5.4% (3/56).

The analyzed group demonstrated 49 positive cultures in the anal region and the most common strain was *Klebsiella pneumoniae* ESBL (+) 28.6% (14/49). Of the 20 positive urinary tract cultures, *Enterococcus spp.* was detected most often — in 35% (7/20). Five positive nasal cultures were confirmed — three with methicillin-sensitive *Staphylococcus aureus* (MSSA), and one each with *Klebsiella pneumoniae* ESBL (+) and *Streptococcus pneumoniae*. Three positive tests from the throat were obtained — *Escherichia coli* ESBL (+), *Klebsiella pneumoniae* ESBL (+), and *Enterococcus faecium*.

The total number of pathogens responsible for colonization was 77 (73 positive bacterial cultures and four positive fungal cultures). Among bacterial cultures, 50.7% (37/73) were caused by MDR strains. The most common type of resistance was ESBL, accounting for 81.1% (30/37) of all resistance types (Table II).

Evaluation of colonization in post-transplant period

In 27% (10/37) of patients colonized before allo-HSCT, there was a change in the result of the weekly post-transplant colonization assessment. In 16.2% (6/37) of patients, there was an eradication of the originally colonizing pathogen. In 10.8% (4/37) of patients, colonization from the urinary tract was eradicated, and the following pathogens were erased: *Escherichia coli* ESBL (+), *Klebsiella pneumoniae*, and *Enterococcus spp*. In 5.4% (2/37) of patients, disappearance of colonization from the nasal cavity with *Streptococcus pneumoniae* and *Staphylococcus*

Table II. Etiology of colonizing pathogens before hematopoietic stem cell transplantation (HSCT) depending on location*

Location of colonization	Etiology of colonization	Positive colonization culture, n [%]
Anal area		49 (100)
	Klebsiella pneumoniae ESBL (+)	14 (28.6)
	Escherichia coli ESBL (+)	8 (16.3)
	Enterococcus faecium	7 (14.3)
	Enterococcus faecalis	7 (14.3)
	Enterococcus faecium GRE	3 (6.1)
	Escherichia coli ESBL (–)	3 (6.1)
	Enterobacter cloacae ESBL (+)	2 (4)
	Candida albicans	2 (4)
	Candida krusei	1 (2.1)
	Candida glabrata	1 (2.1)
	Staphylococcus haemolitycus	1 (2.1)
Urinary tract		20 (100)
	Enterococcus spp.	7 (35)
	Coagulase-negative staphylococci	5 (25)
	Escherichia coli ESBL (+)	3 (15)
	Enterobacteriaceae	1 (5)
	Escherichia coli ESBL (–)	1 (5)
	Klebsiella pneumoniae ESBL (+)	1 (5)
	Streptococcus agalactiae	1 (5)
	Serratia marcescens	1 (5)
Nasal cavity		5 (100)
	Staphylococcus aureus MSSA	3 (60)
	Klebsiella pneumoniae ESBL (+)	1 (20)
	Streptococus pneumoniae	1 (20)
Pharynx		3 (100)
	Klebsiella penumoniae ESBL (+)	1 (33.3)
	Enterococcus faecium	1 (33.3)
	Escherichia coli ESBL (+)	1 (33.3)

*In 15 (34.1%) patients before allogeneic HSCT, the location was colonized by > 1 pathogen; ESBL — extended-spectrum beta-lactamases; GRE — glycopeptide-resistant enterococci; MSSA — methicillin-sensitive *Staphylococcus aureus*

aureus MSSA was observed. On the other hand, three patients had a change in Gram-negative bacteria in the evaluation of colonization from the anus. The first of these patients had a change from *Escherichia coli* to *Klebsiella pneumoniae*, the second from *Klebsiella pneumoniae* to *Escherichia coli* ESBL (+), and the third from *Enterobacter cloacae* to *Escherichia coli*. In one case, a new pharyngeal colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) was detected. Among patients who were not colonized before allo-HSCT, we did not observe the appearance of bacterial colonies during the routine evaluation of colonization after allo-HSCT.

Infection evaluation

Post-transplantation infections occurred up to 100 days after allo-HSCT in 86.4% (38/44) of patients. Among patients with fever, of which the median duration was four days, microbiologically documented infections were found in 71.1% (27/38) of patients, fever of unknown origin (FUO) in 26.3% (10/38), and only clinically documented infection

Table III. Location and etiology of infections caused by colonizing pathogen

Number of patients colonized before allo-HSCT				N = 37
Number of patients with at least one infection with colonizing pathogen [%]				22/37 (59.5%)
Etiology	Location of colonization		Location of infection	Number of infections with a pathogen detected in colonization
Escherichia coli ESBL (+)	Anus	→	Urinary tract	8
	Anus	→	Vascular bed	2
	Anus	→	Gastrointestinal tract	1
Enterococcus faecium	Anus	→	Urinary tract	7
	Anus	→	Vascular bed	1
Klebsiella pneumoniae ESBL (+)	Anus	→	Urinary tract	2
	Anus	→	Vascular bed	1
	Anus	→	Gastrointestinal tract	1
	Urinary tract	→	Urinary tract	1
	Urinary tract	→	Vascular bed	1
Staphylococcus epidermidis MRCSNE	Urinary tract	→	Vascular bed	2
	Anus	→	Urinary tract	1
Enterococcus faecalis	Anus	→	Vascular bed	1
	Anus	→	Urinary tract	1
Candida krusei	Anus	→	Urinary tract	1

allo-HSCT — allogeneic hematopoietic stem cell transplantation; ESBL — extended-spectrum beta-lactamases; MRCNSE — methicillin-resistant coagulase-negative *Staphylococcus epidermidis*

in 2.6% (1/38). Mucositis occurred in 93.2% (41/44) of patients, whereas pneumonia occurred in 9.1% (4/44) of patients.

The total number of pathogens responsible for infections was 138 (105 positive bacterial cultures, 16 positive fungal cultures, and 17 viral infections). On average, there were 3.1 infection factors per patient (138 infections in 44 patients).

Bacterial infections

There were 105 microbiologically confirmed positive bacterial cultures detected up to 100 days after allo-HSCT. Gram-positive infections predominated, accounting for 76.2% (80/105) of all bacterial infections in this group. MDR pathogens were observed in 58.1% (61/105). ESBL was the most common type of resistance, making up 50.8% (31/61).

59.5% (22/37) of colonized patients developed a total of 31 infections with the pathogen responsible for their previous colonization. Infections with such pathogens were significantly more frequent in colonized patients than with *de novo* pathogens ($p = 0.04$). It is worth underscoring the frequent occurrence of bacteremia caused by pathogens that were detected in the colonization of the anal area before allo-HSCT. More detailed information on infections with the pathogen that was previously found in colonization is set out in Table III.

Bacteremia occurred in 47.7% (21/44) of allo-HSCT patients, of which central line-associated bloodstream infections (CLABSI) were noted in 27.3% (12/44) of patients. Bacteremia accounted for 25.8% (8/31) of all infections identified with a pathogen that had been detected previously in colonization. In 20.5% (9/44) of patients, cultures showed more than one pathogen responsible for the blood infection. In total, 33 positive blood cultures were noted. MRCNSE, which accounted for 39.4% (13/33) of etiological factors, was most frequently isolated.

The skin and soft tissue in the region of the central vascular catheter were infected in 27.3% (12/44) of patients. There were 13 positive cultures, and the main etiological agent was MRCNSE, accounting for 38.5% (5/13) of pathogens infecting this area.

Urinary tract infections occurred in 56.8% (25/44) of patients, and the most common etiological factor was *Escherichia coli* ESBL (+), responsible for 25.9% (7/27) of positive cultures in this area.

Positive stool cultures were observed in 38.6% (17/44) of patients. Infection with *Clostridioides difficile* occurred in 15.9% (7/44) of patients (Table IV).

Fungal infections

Fungal infections occurred in 31.8% (14/44) of patients up to 100 days after allo-HSCT. Sixteen positive cultures

Table IV. Etiology of infection after hematopoietic stem cell transplantation in relation to number of positive cultures

Location of infection	Type of infection	Etiology of infection	Positive cultures [%]
Gastrointestinal tract			48 (100)
	Gram-positive bacteria	*Enterococcus faecium*	8 (16.7)
		Clostridioides difficile	7 (14.5)
	Gram-negative bacteria	*Klebsiella pneumoniae* ESBL (+)	9 (18.8)
		Escherichia coli ESBL (+)	7 (14.5)
		Escherichia coli ESBL (–)	3 (6.3)
	Fungi	*Candida albicans*	6 (12.5)
		Candida glabrata	5 (10.4)
		Candida krusei	3 (6.3)
Bacteremia			33 (100)
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	13 (39.4)
		Enterococcus faecium	3 (9.1)
		Staphylococcus hominis MRCNS	2 (6.2)
		Staphylococcus haemolyticus	2 (6.2)
		Staphylococcus spp. MLS_B (+)	1 (3)
		Staphylococcus epidermidis MSCNS	1 (3)
		Streptococcus miti	1 (3)
		Enterococcus faecalis	1 (3)
		Actinomyces naeslundii	1 (3)
		Corynebacterium jeikeium	1 (3)
		Granulicatella adiacens	1 (3)
	Gram-negative bacteria	*Escherichia coli* ESBL (+)	3 (9.1)
		Escherichia coli ESBL (–)	1 (3)
		Klebsiella pneumoniae ESBL (+)	1 (3)
		Pseudomonas aeruginosa	1 (3)
Urinary tract			27 (100)
	Gram-positive bacteria	*Enterococcus faecium*	3 (11.1)
		Enterococcus spp.	2 (7.4)
		Enterococcus faecalis	1 (3.7)
		Enterococcus faecalis HLGR	1 (3.7)
		Enterococcus raffinosus	1 (3.7)
	Gram-negative bacteria	*Escherichia coli* ESBL (+)	7 (26)
		Escherichia coli ESBL (–)	5 (18.5)
		Klebsiella pneumoniae ESBL (+)	5 (18.5)
	Fungi	*Candida krusei*	2 (7.4)
Skin and soft-tissue of the central line area			13 (100)
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	5 (38.4)
		Staphylococcus epidermidis MSCNS	2 (15.4)
		Staphylococcus hominis MRCNS	2 (15.4)
		Enterococcus spp.	2 (15.4)
		Staphylococcus aureus MSSA	2 (15.4)

ESBL — extended-spectrum beta-lactamases; MRCNSE — methicillin-resistant coagulase-negative *Staphylococcus epidermidis*; MRCNS — methicillin-resistant coagulase-negative *Staphylococcus*; MLS_B — resistance to macrolides, lincosamides and streptogramin B; MSCNS — methicillin-susceptible coagulase-negative *Staphylococcus*; HLGR — high-level gentamicin-resistant; MSSA — methicillin-sensitive *Staphylococcus aureus*

were observed. Of these 16, 87.5% (14/16) affected the gastrointestinal tract and 12.5% (2/16) were observed in the urinary tract. The most common etiology of fungal infections was *Candida albicans* 37.5% (6/16), whereas 62.5% (10/16) of fungal infections were associated with resistant strains [*C. krusei* 31.3% (5/16); *C. glabrata* 31.3% (5/16)] (Table IV).

Microbiologically confirmed viral reactivation

Viral reactivation was reported in 29.5% (13/44) of initially seropositive patients during the first 100 days after allo-HSCT. In 6.8% (3/44) of patients, more than one virus was reactivated. CMV reactivation was observed in 22.7% (10/44), EBV in 13.6% (6/44), and HSV in 2.3% (1/44) of patients.

Treatment outcome

The median duration of empirical and targeted antibiotic therapy in patients after allo-HSCT was 24 (range 22–28) and 26 (range 20–34) days, respectively. We showed that patients colonized initially with at least one pathogen had significantly longer fever durations (mean: 4.18 days, SD: 2.96) compared to non-colonized patients (mean: 1.71 days, SD: 2.14) (p = 0.01). Colonization at three or more sites was associated with a longer duration of fever (p = 0.04).

The median overall survival (mOS) for all patients after allo-HSCT included in our study (n = 44) was 52.8 months (95% CI: range 19–56 months), and the median follow-up was 74 months. We found no differences in mOS between colonized patients and non-colonized patients (p = 0.33). For patients with MDR pathogen infection, mOS was 32 months (95% CI: 15–56 months), while mOS for patients without MDR infection was not reached (p = 0.352). The presence of CMV reactivation did not affect OS (p = 0.89), whereas patients with EBV reactivation showed almost halved 2-year survival compared to patients without EBV reactivation (33% vs. 61%), as well as worse mOS (15 months, 95% CI: 5–44 months vs 56 months, 95% CI: 21–56 months) (p = 0.03). Moreover, shorter mOS was observed in patients with candidiasis (30 months, 95% CI: 9–53) vs those without (56 months, 95% CI: 19–56), but the differential trend was marked after a longer follow-up and showed no statistical significance (p = 0.213).

In univariate survival analysis, the variables significantly affecting OS were the age of the patient at the time of allo-HSCT (older patients survived for a shorter time, HR: 1.04, 95% CI: 1.01–1.08, p = 0.01), EBV reactivation (HR: 2.70, 95% CI: 1.05–6.94, p = 0.03), and pneumonia (HR: 3.87, 95% CI: 1.41–10.64, p = 0.01). Hospitalization days demonstrated a tendency towards OS but did not show a statistical significance (HR: 1.06, 95% CI: 0.99–1.13, p = 0.08). In the multivariate regression model, the age of the patient at the time of allo-HSCT (HR: 1.06, 95% CI: 1.02–1.11, p = 0.01), as well as EBV reactivation (HR: 6.03, 95% CI: 1.96–18.54, p = 0.002) and the occurrence of pneumonia (HR: 4.01, 95% CI: 1.28–12.56, p = 0.02) proved to be independent factors significantly worsening OS.

Death occurred in 13.6% (6/44) of patients within 100 days after allo-HSCT. Four of these six patients died in the course of bacteremia and two of acute GvHD.

Discussion

We present a comprehensive analysis of the colonization of patients undergoing allo-HSCT and its impact on post-transplantation infectious complications. To the best of our knowledge, there has been no previous study in the literature analyzing the etiology and frequency of colonization of all sites, such as urine, throat, nasal cavity, and anal area, which were subject to standardized microbiological evaluation before allo-HSCT, and its influence on patient outcomes.

In our study, colonization before allo-HSCT with at least one pathogen was found in 84.1% of patients, while MDR bacteria accounted for half (50.7%) of all positive colonization cultures. The analysis conducted by Scheich et al. [12] in 264 patients who underwent allo-HSCT between 2006 and 2016 demonstrated that colonization of the anus, nasal cavity, and throat with multi-drug resistant flora occurred in 53.8% of patients, which is consistent with our observations. However, preliminary data from our team's prospective analysis from 2022 in 239 allo-HSCT recipients shows a decrease in the amount of MDR pathogens, which accounted for 29% of colonization cultures [13]. Another European study by Bilinski et al. [14] revealed MDR bacteria colonization after allo-HSCT in 31% of patients, although only gastrointestinal tract colonization was evaluated.

Infections are the most common and significant cause of stem cell transplant failure, as well as mortality, after allo-HSCT [6]. They are associated with a specific cascade of immune dysfunction, the reconstruction of which can take up to several years after the HSCT procedure. The regeneration of individual elements of the immune system proceeds with different dynamics, with innate immunity (neutrophils, monocytes, and natural killer cells) usually preceding adaptive immunity (T and B lymphocytes) [15–17].

We determined the number and type of infections involved in the post-transplantation period, which occurred in 86.4% of patients. Analysis conducted by Schuster et al. [18] on 431 patients undergoing allo-HSCT between 2006 and 2011 revealed the presence of infection in 93% of patients. The number of infections after allo-HSCT observed in our analysis is similar to the results received in other transplantation centers in Poland and worldwide, where, despite applied anti-infection prevention, infections occur frequently in 80–100% of patients [18–20].

We found the presence of bacteremia in 47.5% of patients, which is similar to other centers. Schuster et al. [18] noted bacteremia in 53% of patients after allo-HSCT. In the analysis conducted between 2008 and 2013 by Gjaerde et al. [21] on 460 patients undergoing allo-HSCT, bacteremia was observed in 34% and 17% of patients after MAC and reduced toxicity conditioning (RIC), respectively.

In our study, CLABSI was observed in 27.3% of patients after allo-HSCT. Mariggiò et al. [22] reported CLABSI in 32% of patients after allo-HSCT. The results obtained in our study are comparable to those presented by other researchers [22, 23].

Neutropenic fever (FN) complicates more than 80% of severe chemotherapy-induced neutropenia, and 50–60% of these patients go on to develop FUO, whereas microbiological detection of infection is possible in only 10–20% of patients, and clinically documented in 20–30% [24]. The mortality rate associated with FN is c.10%, but in cases of severe infection or septic shock, it can reach 50% [25]. Patients with profound neutropenia, defined as ANC less than 0.1 G/L, represent the group at highest risk. Bacteremia then occurs in 20% and can progress with septic shock and multiple organ failure [26].

There are two main sources of bacterial infections in the early phase before allo-HSCT. The endogenous flora of the gastrointestinal tract is mainly responsible for Gram-negative bacterial infections as a result of treatment-related mucosal damage. Secondly, exogenous nosocomial microorganisms, which are often associated with catheter-related infections, are predominantly Gram-positive bacteria. The incidence of Gram-positive bacterial infections has been increasing since the 1980s. However, Gram-negative bacterial infections are still associated with high mortality rates, and the incidence of infections with MDR strains has been increasing over the past decade [17, 27]. In our cohort, Gram-positive bacteria also predominated, accounting for 76.2% of all positive cultures from infected sites, and most often we observed coagulose-negative *Staphylococci*. Contrary to some other studies, Gram (–) bacteria constituted a minority in our center — 23.8% [28–30]. Meanwhile, an analysis by Girmenia et al. [31] of 1,118 patients after allo-HSCT assessed the cumulative incidence of pre-engraftment Gram (–) bacteremia to be 17.3% of patients and 13.2% as for Gram (+). Observations made by Mikulska et al. [28] in a 2004–2007 study of 132 patients undergoing allo-HSCT showed a decrease in the ratio of Gram (+)/Gram (–) bacteria in cultures from the vascular bed in subsequent years of the study — 68%/28% (2004) vs. 48%/48% (2007). However, in our center, there is still a trend of significant predominance of Gram (+) bacteremia over Gram (–) etiologies.

Over the last dozen or so years, the number of MDR infections has significantly increased, thus creating numerous problems for effective antibiotic therapy. In our study, MDR pathogens accounted for 58.1% of bacterial etiological factors after allo-HSCT. Our literature review did not find a multi-drug resistance analysis covering multiple locations of infection and different types of resistance simultaneously. Mikulska et al. [28] analyzed Gram-negative MDR bacteria, which constituted 35% of all Gram-negative infectious bacteria isolated in the vascular bed in patients after allo-HSCT. In a multicenter analysis, Averbuch et al. [32] evaluated the Gram-negative bacteria resistance of 414 recipients of allo-HSCT and 241 recipients of auto-HSCT between 2014 and 2015. The percentages of Gram-negative MDR rods were 44% and 20% for the allo-HSCT and auto-HSCT groups, respectively [32].

Invasive fungal infections are an important type of infection complication associated with the transplantation procedure. In our analysis, infection with at least one fungal pathogen occurred in 31.8% of patients after allo-HSCT, the most common pathogen being *Candida albicans*. A study conducted by Shi et al. [33] in 408 patients undergoing allo-HSCT detected the presence of fungal infection in 22.5% of analyzed patients. *Candida* was the most common pathogen for early fungal infection, and *Aspergillus* was the most frequent causative organism for late fungal infection.

Yeast, which causes an infection called candidiasis, enters the body by translocation through catheters or damaged intestinal mucosa, unlike mold, which enters the body by the inhalation of airborne spores. Due to the suppression of cellular immunity, phagocytosis of these pathogens by macrophages is impaired, allowing their reproduction [17, 34]. In our study, *Candida spp*. was responsible for 100% of all fungal pathogens, headed by *C. albicans* — 37.5%. An analysis by Kontoyiannis et al. [35], conducted on 16,200 patients after auto- and allo-HSCT between 2001 and 2006, showed that among invasive fungal infections, 43% were invasive aspergillosis and 28% were invasive candidosis. *C. glabrata* (33%) and *C. albicans* (20%) cultures predominated in the group of candidiasis [35].

According to scientific reports, the incidence of aspergillosis and infections caused by *Candida spp.*, and in particular by *C. albicans*, has decreased in recent years, due to widely conducted prophylactic and therapeutic activities, including the use of second-generation azoles [36].

On the other hand, intensive prophylaxis has contributed to an increase in the incidence of resistant strains such as *C. glabrata* or *C. krusei* [36–38]. In a study by Kontoyiannis et al. [35], *C. glabrata* and *C. krusei* accounted for 33% and 6%, respectively, among invasive candidiasis. It is worth noting that among allo-HSCT recipients of our study, 62.5% of fungal infections were associated with resistant strains [*C. krusei* 31.3% (5/16); *C. glabrata* 31.3% (5/16)].

Both our previous [39] and our current observations, as well as those of Hierlmeier et al. [40] and Pagano et al.

[41], show a disproportion between the incidence of fungal infections depending on the type of transplantation, in favor of allo-HCT.

Some of the most important causes of mortality and morbidity after allo-HSCT are related to viral reactivations. In our study, the reactivation of at least one viral agent in patients originally seropositive was reported in 29.5% of patients. An analysis of the first 100 days after allo-HSCT confirmed reactivation of CMV in 22.7%, EBV in 13.6%, and HSV in 2.3% of patients, respectively. A study including 65 patients undergoing allo-HSCT, performed by van Esser et al. [42], revealed that EBV reactivation occurred in 28% (day range: 2 + 107). However, Walker et al. [43] revealed CMV reactivation in 22% of 753 patients undergoing allo-HSCT (day range: 0 + 182). It is important to underscore that in our cohort the incidence of viral reactivation might be higher given the longer follow-up.

With regards to the total number of infectious pathogens detected in patients of our center in the post-transplantation period, there were on average 3.1 infectious factors per patient in the allo-HSCT group. Compared to an earlier analysis at our center, which looked at patients after auto-HSCT, this is twice as much for allo-HSCT compared to auto-HSCT (3.1 vs. 1.5) [39].

Colonization, mainly with MDR pathogens, contributes to an increased risk of infection and reduces the effectiveness of subsequent antibiotic therapy, thus posing a threat to the effective regeneration of the hematopoietic system. In our center, 59.5% of patients who appeared to be colonized before allo-HSCT could not avoid at least one infection with a colonizing pathogen. As far as infections with a pathogen detected in colonization are concerned, allo-HSCT recipients were most frequently affected by urinary tract infections with pathogens of previous anal colonization, mostly *Klebsiella pneumoniae* ESBL (+) and *Escherichia coli* ESBL (+). Moreover, recent studies have highlighted the importance of colonizing gut microbiota in the prognosis after allo-HSCT and the role of fecal microbiota transplantation as a potential therapeutic option in cases of microflora dysfunction, primary gastrointestinal colonization with MDR bacteria, or acute gastrointestinal GvHD [44, 45].

In our study, infections after allo-HSCT caused by pathogens that were detected in colonization before allo-HSCT were almost 10 times more common compared to an earlier analysis of auto-HSCT recipients at our center (59.5% vs. 6.4%) [39].

Conclusions

Despite the development of modern preventive strategies, and a better understanding of the mechanisms of immunosuppression, the problem of post-transplantation infections is still an unmet clinical challenge. Assessment of colonization and infections in the peri-transplant period should be carried out systematically. Such management allows optimal selection of prophylaxis and empirical therapy for neutropenic fever, and potentially translates into faster implementation of targeted therapy and improvement of infection outcomes.

Our study has demonstrated that infections with a colonizing pathogen can be observed after allo-HSCT. This is most likely due to a longer period of marrow aplasia, mechanical damage to mucosal barriers, more intensive immunosuppressive treatment, and frequent development of GvHD in allogeneic transplant recipients.

The results of the presented study highlight the role of colonization assessment as a tool for identifying patients at high risk of developing post-transplant infections, thus providing an opportunity for prompt targeted antibiotic therapy.

Article information and declarations

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Author contributions
All authors contributed to study conception and design. Material preparation, data collection and analysis performed by KK, PS, KS, MC, AS, OGI, AW and AP. First draft of manuscript was written by KK, and all authors commented on subsequent versions of manuscript. All authors read and approved final manuscript.

Conflict of interests
The authors declare no conflict of interests.

Data availability statement
The datasets generated during and/or analyzed during the current study are not publicly available due to the fact that individual privacy could be compromised, but are available from the corresponding author upon reasonable request.

Ethics statement
This study was performed in line with the principles of the Declaration of Helsinki. This research study was conducted retrospectively from data obtained for clinical purposes. Informed consent was obtained from all individual participants included in the study.

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Supplementary material

None.

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