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Research article

RISK FACTORS OF HEALTHCARE-ASSOCIATED INFECTIONS IN RECIPIENTS OF BONE MARROW TRANSPLANT

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Bone marrow recipients are the most immunocompromizied patients who are susceptible to multiple infections. It is especially true for long-term episodes of drug-associated granulocytopenia.

Our research goal was to identify risk factors of healthcare-associated infections (HAIs) in patients after bone marrow transplantation (BMT).

Risk factors of developing HAIs were identified by accomplishing an analytical epidemiological "case – control" study with 973 patients participating in it. They all underwent BMT in the Hematology, Chemotherapy and Bone Marrow Transplantation Department of the Pirogov National Medical and Surgical Center on a period from 2015 to 2018. The following diseases were diagnosed in them: lymphoma (n = 158), multiple myeloma (n = 96), and multiple sclerosis (n = 719). HAIs cases were selected based on the standard (epidemiological) case definition in accordance with the Federal Clinical Recommendations on Epidemiological Surveillance over HAIs approved by the National Association of Experts responsible for Control over Healthcare-Associated Infections.

Retrospective analysis established 75 HAIs cases or 7.7 % of the total number of the analyzed patients after BMT. Catheter-related bloodstream infections took the leading place among all the HAIs accounting for 52.0 ± 2.4 %. They were followed by bloodstream infections, 28.0 ± 3.1 %; lower respiratory tracts infections, 17.0 ± 3.2 %; and post-injection complications, 3.0 ± 0.6 %. Oncological diseases were established to cause HAIs in bone marrow recipients more frequently (OR = 5.603; 95 % CI = 3.422–9.174) than multiple sclerosis (OR = 0.178; 95 % CI = 0.109–0.292). This indicates that an underlying disease has its influence on a risk of infectious complications. We established a direct correlation between HAIs frequency and contamination with opportunistic microorganisms detected in objects in the hospital environment (r = 0.79, p = 0.01). This calls for implementing up-to-date disinfection provided for such objects.

Keywords: *bone marrow transplantation, healthcare-associated infections, febrile neutropenia, mucositis, risk factors.*

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Healthcare-associated infections (HAIs) are among the most pressing multidisciplinary issues in contemporary healthcare. This is due to their wide prevalence and their grave negative outcomes for patients' health, health workers and a country economy[1] [1–4].

A medical organization examines HAIs-related issues within the risk-based approach [5, 6] depending on its profile and applied technologies. The approach highlights the necessity to determine patient groups that are the most susceptible to risks of HAIs. Bone marrow recipients (BMR) are among patients with high risks of HAIs considering their long-term in-hospital treatment and long-term episodes of drug-associated granulocytopenia[2] [7]. According to the latest research, cumulative infectious incidence among BMR equals 10.5 % (95 % CI: 12.0–25.8 %) after allogeneic transplantation. Fifty-seven percents of these infection cases occur during a period when a patient suffers from severe neutropenia (neutrophils contents are $< 0.1 \cdot 10^6$ units/l) or pancytopenia [8]. Lethality can reach 60 % in case of developing infectious complications [9–11].

Most frequently, HAIs as well as bacteremia are induced by opportunistic microorganisms. They occur everywhere and are well-known representatives of skin, mucosa and GUT microflora[1]. At present, microorganisms from ESCAPE-pathogen[3] group are more and more frequently identified as HAIs agents.

Up-to-date infection diagnostic procedures and use of broad-spectrum antibacterial drugs make development of severe infectious complications as well as a fatal outcome much less likely [11]. However, cellular and humoral immunity in bone marrow recipients with neutropenia is not able to react adequately when an infectious agent penetrates the body. Given that, a septic shock can develop quite rapidly in such patients skipping all the previous stages in sepsis development [10].

Therefore, patients after bone marrow transplantation (BMT) have elevated risks of HAIs [10, 12, 13]. At the same time, studies that focus on determining risk factors that cause HAIs in such patients are scarce and rather contradictory.

Our research goal was to determine risk factors of healthcare-associated infections in patients after bone marrow transplantation.

Materials and methods. HAIs cases were detected by using a diagnostic card, which we developed ourselves. It was done based on retrospective active searching for purulent septic infections in 973 patients. They were treated in the Hematology, Chemotherapy and Bone Marrow Transplantation Department of the Pirogov National Medical and Surgical Center (the Hematology Department) in a period from 2015 to 2018. All the examined patients underwent bone marrow transplantation due to the following diagnosed diseases: lymphoma (n = 158), multiple myeloma (n = 96), and multiple sclerosis (n = 719). In our study, we applied the standard epidemiological case definition in accordance with the Federal Clinical Recommendations on Epidemiological Surveillance over HAIs approved by the National Association of Experts respon-

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sible for Control over Healthcare-Associated Infections[4].

Risk factors of HAIs were established by accomplishing an analytical epidemiological "case – control" study.

Our test group was made up of 75 patients who had signs of various HAIs during their in-hospital treatment. The reference group included 898 patients without any registered HAIs during one month after bone marrow transplantation.

Influence exerted by contamination of objects in the hospital environment on HAIs occurrence and development was accomplished in dynamics by analyzing correlations between incidence of HAIs among patients and contamination of external objects surrounding them in a hospital. Contamination levels were established as per results produced by scheduled sanitary-bacteriological examinations that were accomplished in the Hematology Department in 2015–2018.

All the data were statistically analyzed with parametric and non-parametric statistical procedures. Initial data were accumulated, corrected and systematized and the obtained results were visualized with Microsoft Office Excel 2016 and Medstatistic.ru calculator.

In case quantitative characteristics were distributed normally, we applied Student's t-test for two independent samplings to analyze them and the results were given as a simple mean (M) ± standard error of mean (m).

We calculated odds ratio (OR) of HAIs depending on whether risk factors were present or absent as per results of building up a fourfold table according to the formula $A \cdot D/B \cdot C$. The indicator was considered positive if its value was > 1. Differences were considered authentic if a confidence interval for this indicator did not include unity.

We applied Pearson's χ^2 test to reveal statistical significance of differences in qualitative characteristics. In this study, the critical significance level was taken as equal to 0.05 ($p \leq 0.05$).

Results and discussion. The analysis revealed 75 HAIs cases; the quantity equaled 7.7 % of the overall number of bone marrow recipients over the analyzed period.

Catheter-related bloodstream infections took the leading place among the detected HAIs accounting for 52.0 ± 2.4 %. They were followed by bloodstream infections, 28.0 ± 3.1 %; lower respiratory tract infections, 17.0 ± 3.2 %; and post-injection complications, 3.0 ± 0.6 %. These data are consistent with results produced by some Russian and foreign studies[3, 5] [7, 11, 12].

We estimated cause-effect relations between a supposed risk factor and HAIs development in a patient. Our estimates established certain differences from previously published data (Table).

Therefore, we did not establish any statistically authentic correlation between a patient's age and HAIs frequency; although, it seems only logical that, considering how physiological immune deficiencies tend to develop, the older a patient is, the higher likelihood of severe complications after BMT is. We did not establish any sex-dependent difference in HAIs development either.

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Risk factors of HAIs in bone marrow recipients

Risk factor	Likelihood		Odds ratio	95 % CI	χ^2
	in the test group	in the reference group			
Sex:					
male	0.829	0.666	1.245	0.775–2.000	0.825
female	1.206	1.501	0.803	0.500–1.290	0.825
Age, years:					
younger than 20	0.014	0.015	0.920	0.119–7.130	0.006
20–30	0.190	0.166	1.146	0.601–2.184	0.171
30–40	0.364	0.439	0.828	0.487–1.409	0.485
older than 40	1.273	1.164	1.094	0.680–1.757	0.137
Underlying disease:					
oncological	1.679	0.300	5.603	3.422–9.174	56.314
multiple sclerosis	0.596	3.338	0.178	0.109–0.292	56.314
BMT complications:					
mucositis	0.563	0.244	2.308	1.400– 3.802	11.800
febrile neutropenia	4.357	0.691	6.304	3.474–11.440	46.001

We analyzed frequency of HAIs depending on an underlying disease and established that complications were much more likely in patients with oncological diseases (lymphoma and multiple myeloma): 1.679 (*OR* = 5.603; 95 % CI: 3.422–9.174) against 0.596 (*OR* = 0.178; 95 % CI: 0.109–0.292) in patients with multiple sclerosis.

Infectious complications develop after transplantation largely depending on how inhibited the hematopoietic and immune systems are in a given patient[6] [14, 15] when he or she is being prepared for transplantation with cytostatic therapy. This therapy often induces mucositis (necrotic lesions in GUT mucosas) [16–18] and this is a predisposing factor of developing infections. We established that HAIs frequency amounted to 0.563 among patients with mucositis whereas it equaled 0.244 in the reference group (patients without this pathology) (*OR* = 2.308, 95 % CI: 1.400–3.802). This indicates that endogenous infection often acts as an inducer of developing complications in patients after BMT.

Results produced by multiple research works indicate that febrile neutropenia rather frequently develops in an early post-transplantation period. It can be viewed as a marker of subsequent HAIs development [19–21] as it was confirmed by the results produced by the present study. Thus, frequency of febrile neutropenia equaled 4.357 in the test group against 0.691 in the reference one (*OR* = 6.304, 95 % CI: 3.474–11.440). This makes it possible to consider this clinical sign a criterion of early HAIs diagnostics in patients after BMT.

High contamination with infectious agents detected in objects in the hospital environment is a well-known risk factor that can cause HAIs in patients [21, 22].

We estimated results produced by sanitary-bacteriological control of external objects in the Hematology Department (816 wash-offs); samples were established positive in 12.5 % of the cases. Several groups of microorganisms were detected the most frequently including coagulase-negative staphylococcus (80.4 %), Pseudomonas aeruginosa

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(8.8 %), Staphylococcus aureus (3.9 %), and Enterococcus faecalis (3.9 %).

We established a direct correlation between a growing number of HAIs cases in patients after BMT and levels of contamination with opportunistic microorganisms detected in objects in the hospital environment. The correlation coefficient was equal to 0.79 ($p = 0.01$). This indicated that HAIs agents were spread in the Hematology Department through communal contacts, common items and objects in the hospital environment being the leading transmission factors.

Therefore, effective management of infection risks for patients aimed at reducing them down to their acceptable levels requires constant epidemiological prospect surveillance over bone marrow recipients. This surveillance should involve monitoring of all the aforementioned risk factors.

Conclusions:

1. We established that infectious complications developed in bone marrow recipients in 7.7 % of the cases and that catheter-related bloodstream infections prevailed in the incidence of HAIs accounting for 52.0 ± 2.4 %.

2. Age- and sex-dependent differences are not among risk factors of developing HAIs among bone marrow recipients.

3. An oncological disease in bone marrow recipients as an underlying one is the most significant risk factor of HAIs for bone marrow recipients (*OR* = 5.603; 95 % CI: 3.422–9.174) in comparison with multiple sclerosis (*OR* = 0.178; 95 % CI: 0.109–0.292).

4. Febrile neutropenia in bone marrow recipients should be considered a marker of subsequent HAIs development (*OR* = 6.304; 95 % CI: 3.474–11.440).

5. HAIs agents are actively spread in hematology departments through communal contacts, which is confirmed by the detected correlation between frequency of such infections and microbial contamination of objects in the hospital environment ($r = 0.79$, $p = 0.01$).

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