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Single Positive Commensal Blood Culture in hospital setting is associated with higher mortality after hematopoietic stem cell transplantation

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ABSTRACT

Background: Single positive staphylococcal blood culture in a hematopoietic stem cell transplantation (HSCT) recipient is generally regarded as contamination. Such a blood culture (BC) does not fill the criteria for Laboratory-Confirmed Bloodstream Infection (LCBI) and could be described as Single Positive Commensal Blood Culture. The aim of this retrospective cohort analysis was to determine the clinical significance of SPCBC in HSCT recipients. **Methods:** 206 patients transplanted between 2007 and 2013 were followed until January 2015. **Results:** The 100-day survival for patients without positive BC was 99.6% compared with 83.9% for LCBI and 82.8% for SPCBC ($p = 0.0036$). The 5-year overall survival (5yOS) was 67.1% for patients without positive BC, 44.9% for LCBI, 34.0% for SPCBC ($p < 0.0001$). The per-day risk of developing SPCBC was identical in autologous and allogenic transplantation. SPCBC remained a significant factor for reduced 5yOS after HSCT in the univariate analysis (HR 2.52, 1.26–5.02, $p = 0.0001$) as well as in the multivariate analysis (HR 2.21, 1.26–3.87, $p = 0.006$). SPCBC consisted solely of different *Staphylococcus* species with dominance of *Staphylococcus epidermidis* (64% of SPCBC). **Conclusion:** To our knowledge this is the first report that specifically shows that short- and long-term survival after HSCT is significantly lower in patients who experience an episode of SPCBC with *Staphylococcus* spp. during HSCT hospitalization.

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Introduction

Bloodstream infections (BSI) are a major risk of severe complications for patients after hematopoietic stem cell transplantation (HSCT) [1–4]. *Staphylococcus* spp. bacteria are part of the normal skin flora and are regarded as one of the leading causes of nosocomial infections [5, 6]. Even though Staphylococci are found in a significant proportion of blood cultures collected from patients after HSCT, their presence is often underestimated. Moreover, there are no separate analyses of survival of patients with staphylococcal BSI after HSCT in current studies [1–3]. The role of staphylococcal BSI is more acknowledged in neonatal late onset sepsis, which is most often associated with indwelling medical devices [7]. In infants with very low birth weight, mortality rates for *Staphylococcus epidermidis* BSI, for example, range from 1.5% to 10.2%, showing that bloodstream infection by this pathogen cannot be simply regarded as a "contamination".

European Centre for Disease Prevention and Control (ECDC) and Centres for Disease Control and Prevention (CDC) diagnostic criteria of Bloodstream Infection (BSI), Laboratory-Confirmed Bloodstream Infection (LCBI) or Central Line Associated Bloodstream Infection (CLABSI) require at least two positive blood cultures with common skin contaminant, e.g. *Staphylococcus* spp., for the diagnosis to be established [8, 9]. A single positive culture with *Staphylococcus epidermidis* in HSCT patient (with or without symptoms of infection) under current guidelines is not classified as BSI or LCBI. For the purpose of this analysis we classified those cases as Single Positive Commensal Blood Cultures (SPCBC) – a definition that would include all cases of patients with single commensal cultures, with or without other clinical symptoms of infection.

Due to the clinical characteristics of some patients with SPCBC during the HSCT hospitalization, we hypothesized that SPCBC within this group of patients might influence the outcome of transplantation.

In this publication, we show that the HSCT patients who have an episode of SPCBC (i.e. a single positive blood culture of *Staphylococcus* spp.) during the transplant hospitalization, have significantly higher short- and long-term mortality. While all of those cases did not fulfil the criteria for BSI, LCBI or CLABSI, we were able to show their significant influence on outcome after HSCT.

Patients and methods

This study was a retrospective cohort analysis of consecutive adult patients who underwent autologous or allogeneic haematological stem cell transplantations at the Department of Haematology, Oncology and Internal Medicine of the Medical University of Warsaw.

In 2006 we set up an electronic medical record system for storing the hematopoietic stem cell transplantation recipients' information. It recorded data necessary for EBMT and CIMBTR reports and excerpts from patients' discharge summaries – including significant microbiological data – that could be systematically evaluated. This allowed us to gather clinical information about patients after standard hematopoietic stem cell transplantation which exceeded the basic standards required for EBMT and CIMBTR data reporting.

Patients' data were collected and entered into the database between December 2006 and March 2013. After concluding an internal audit that excluded incomplete or incompatible records, we began the final analysis. Patients' outcomes were followed until their death or the cut-off date of December 31, 2014. Response to therapy, relapse, and survival data were updated continuously. No patients were lost to follow-up. All the information concerning demographics, type of underlying disease, transplant type, and survival was noted. All patients gave written, informed consent allowing the use of their medical records for research. The study was approved by Local Institutional Ethics Board.

Prophylaxis and management of infections

Patients received standard antimicrobial prophylaxis with ciprofloxacin, antiviral prophylaxis with acyclovir, and antifungal prophylaxis with fluconazole during the HSCT hospitalization. Central venous catheters were placed on the first day after admission to the hospital and were removed on the day of discharge. Non-tunnelled double lumen central venous catheters were placed in subclavian vein as a standard in HSCT patients. In cases where CVC had to be removed because of infections, the next CVC has been inserted on the same or next day.

In case of fever (pyrexia of 38 °C) or other signs or symptoms of infection, prophylactic antibiotics were stopped and blood cultures were taken. Patients were treated with broad-spectrum intravenous antibiotics at the discretion of the attending physicians until the results of the bacterial cultures were known. The first line antibiotic therapy standard of the centre was piperacillin/tazobactam with amikacin. Other antibiotics were introduced according to the results of the bacterial cultures. If the patient developed signs of septic shock or the symptoms persisted more than 48 h, meropenem or imipenem/cylastatin were added. Fungal infection diagnostic and treatment has been initiated in cases of persistent fever (>96 h), suspected or confirmed fungal infection. In cases of CMV reactivation patients were treated with ganciclovir or other antivirals. Antibiotics were modified according to the susceptibility of all organisms isolated.

Bloodstream infection

All blood cultures (BC) were obtained in response to clinical suspicion of infection, usually fever (pyrexia of 38 °C), malaise, or rash near the site of central venous catheter insertion, or after physician's request (usually when other clinical signs made infection probable). As a standard two sets (aerobic and anaerobic) of blood cultures were taken – one from periphery and one from central line. If there was no bacterial growth and fever persisted subsequent sets of BC were taken.

Blood specimens were tested using BD BACTEC bottle culture qualitative test. Kirby-Bauer disc diffusion test was

used to assess antibiotic susceptibility and resistance in all cultures. Etest was used when the data on antibiotic susceptibility could not be obtained otherwise. EUCAST guidelines were followed in all steps of microbiological testing [10].

Bloodstream infection (BSI) was defined as presence of any positive bacterial blood culture in a patient. Laboratory-Confirmed Bloodstream Infection (LCBI) was defined in accordance with the guidelines for Bloodstream Infection Event specified by Centres for Disease Control and Prevention as a recognized pathogen identified from one or more blood specimens that was not related to an infection at another site [9]. Single Positive Commensal Blood Culture (SPCBC) was diagnosed in cases of identification of a common commensal (in line with CDC organism list) [11] from one blood culture that was not related to an infection at another site regardless of other symptoms (e.g. fever [>38.0 °C], chills, or hypotension).

The patient was defined as having no bloodstream infection if no bacteria were identified in any blood cultures. An infection was considered polymicrobial if two or more pathogens were isolated from a blood culture.

Definitions

The criterion for engraftment was the first of three days with an absolute neutrophil count of 500/mm^3 or greater as per EBMT guidelines [12]. Acute GvHD was graded according to standard criteria [13]. The maximum grade of acute GvHD that developed in each patient was used.

Statistics

All statistical calculations were done using MedCalc Statistical Software version 15.10 (MedCalc Software bvba, Ostend, Belgium). In all analyses, a p-value of <0.05 was considered statistically significant.

For the comparison between groups of medians of continuous variables, the Mann–Whitney U test was used. For the comparison between groups of categorical variables, the Chi-squared test was used. Univariate survival analysis was performed using Kaplan–Meier survival analysis regression reporting hazard ratios (HR) and 95% confidence intervals (CI). Multivariate survival analysis was performed using Cox proportional hazards regression reporting hazard ratios (HR) and 95% confidence intervals (CI). For multivariate analyses, all variables from univariate analysis that had a p-value less than or equal to 0.05 were included.

When testing acute GvHD, degree of HLA matching or acute myeloid leukaemia as a predictor of mortality, we adjusted for the type of HSCT. This was done in order to minimize the probability of confounding, since, in this cohort, acute myeloid leukaemia was treated only with allogeneic transplantations, and GvHD and HLA matching do not pose a problem when autologous transplantation is performed.

Variables analyzed included age, sex, type of HSCT, HLA matching, acute GvHD, neutropenic fever, cytomegalovirus (CMV) infection reactivation and time to engraftment. Type of blood culture (SPCBC or LCBI) was additionally examined in the mortality analysis.

Results

206 patients with haematological malignancies receiving autologous and allogenic HSCT between 2006 and 2013 were identified for the study. All patients had complete and validated medical records; all of them completed the follow-up and their data were gathered and analyzed. Median time of follow-up was 36 months (range 0.77–80.0).

General characteristics of patients included in the study are listed in Table I. Median time from transplantation to discharge (or death) for all HSCT recipients was 22 days. Hundred-day survival rate was 92.7%, three-year survival rate was 65.7%, while five-year survival rate was 59.1%.

Microbiology

60 (29.1%) patients had at least one positive bacterial blood culture (Tab. I). Thirty-one (15%) patients had a Laboratory-Confirmed Bloodstream Infection while 29 (14.1%) patients had a Single Positive Commensal Blood Culture. There were no patients with both LCBI and SPCBC pathogens. Antibiotic-resistant species were isolated from 16 (7.7%) patients, 8 in the LCBI and 8 in the SPCBC group.

Seventy-one positive microbiologic blood isolates were obtained in total; 9 patients had a positive blood culture with two or more pathogens simultaneously. There were no patients who had a positive blood culture on more than one occasion. Gram-positive bacteria were found in 40 (56.3%) blood cultures and Gram-negative bacteria were found in 31 (43.7%) blood cultures. Pathogens from each group are listed in Table II. The most common pathogen in SPCBC group was *Staphylococcus epidermidis*, which constituted 63.3% of SPCBC isolates and 29.6% of all isolates. *Staphylococcus* spp. species constituted all of SPCBC isolates. There were no fungal isolates.

The frequency of all positive BC was significantly higher in allogeneic HSCT when compared to autologous transplantations (34.9% vs. 13.4%, $p = 0.001$). LCBI were more frequent in the allogeneic transplantation recipients (19.2% vs. 4.3%, $p = 0.0062$), while SPCBC frequency did not differ significantly between allogeneic and autologous transplants (15.8% vs. 8.7%, $p = 0.2099$).

The frequency of antibiotic-resistant species was similar in LCBI and SPCBC patients (25.8% vs. 27.6%, $p = 0.8916$).

The risk of having a positive BC was 1.21% per day of hospitalization; the risk of LCBI was 0.60% per day of hospitalization and the risk of SPCBC was 0.61% per day of hospitalization. There was no statistically significant difference in the risk of having a positive BC per day of hospitalization between allogeneic and autologous HSCT recipients (1.35% vs. 0.91%, $p = 0.158$). Likewise, there was no statistically significant difference in LCBI (0.72% vs. 0.35%, $p = 0.760$) and SPCBC (0.63% vs. 0.56%, $p = 0.760$) per hospitalization day risk between allogeneic and autologous transplant patients.

Table I – General data of the patients included in the study

Characteristics	All patients (%)	No BC (%)	SPCBC (%)	LCBI (%)
Number of patients	206 (100)	146 (70.9)	29 (14.1)	31 (15.0)
Median age on admission (min–max) [years]	37 (18–66)	36 (18–66)	44 (18–59)	44 (20–65)
Median BMI (IQR)	25.0 (22.3, 28)	24.3 (21.6, 27.7)	25.5 (22.6, 28.9)	25.7 (23.6, 28.3)
Gender				
Female	94 (45.6)	68 (46.6)	11 (37.9)	15 (48.4)
Male	112 (54.4)	78 (53.4)	18 (62.1)	16 (51.6)
Type of transplantation				
Autologous	67 (32.5)	58 (39.7)	6 (20.7)	3 (9.7)
Allogeneic	139 (67.5)	88 (60.3)	23 (79.3)	28 (90.3)
Underlying disease				
Acute myeloid leukaemia	67 (32.5)	39 (26.7)	14 (48.3)	14 (45.2)
Other than acute myeloid leukaemia	139 (67.5)	107 (73.3)	15 (51.7)	17 (54.8)
CMV reactivation				
Absent	193 (93.7)	137 (93.8)	27 (93.1)	29 (93.5)
Present	13 (6.3)	9 (6.2)	2 (6.9)	2 (6.5)
HLA match				
10 of 10	190 (92.2)	139 (95.2)	25 (86.2)	26 (83.9)
9 of 10	16 (7.8)	7 (4.8)	4 (13.8)	5 (16.1)
Acute GvHD[a]				
GvHD 0-II	195 (94.7)	141 (96.6)	26 (89.7)	28 (90.3)
GvHD III-IV	11 (5.3)	5 (3.4)	3 (10.3)	3 (9.7)
Neutropenic fever				
Present	86 (41.7)	74 (50.7)	5 (17.2)	7 (22.6)
Absent	120 (58.3)	72 (49.3)	24 (82.8)	24 (77.4)
Time to engraftment (IQR) [days]	15 (12, 19)	14 (11, 18)	18 (13, 22)	16 (14, 20)
Time from transplantation to discharge (IQR) [days]	22 (16, 29)	21 (15, 28)	26 (20, 30)	26 (21, 39)
Overall survival				
Survived	126 (61.2)	101 (69.2)	11 (37.9)	14 (45.2)
Died	80 (38.8)	45 (30.8)	18 (62.1)	17 (54.8)

IQR – interquartile range; BC – blood culture; SPCBC – Single Positive Commensal Blood Culture; LCBI – Laboratory-Confirmed Bloodstream Infection; BMI – body mass index; GvHD – graft versus host disease
[a] Adjusted for the type of HSCT.

Outcome

The median time from transplantation to discharge (and interquartile range) in subjects without positive BC was 21 days (15, 28 days), in subjects who developed LCBI it was 26 days (21, 39 days, $p = 0.0005$), and in subjects who developed SPCBC it was 26 days (20, 30 days; $p = 0.0155$).

Hundred-day survival rate was 99.6% in the patients without positive BC, 83.9% in the LCBI group and 82.8% in the SPCBC group ($p = 0.0036$). Three-year survival rate was 75.0% in the group without positive BC, 44.9% in the LCBI group and 40.8 in the SPCBC group ($p = 0.0004$). Five-year survival rate was 67.1% in the subjects without positive BC, 44.9% in the LCBI group and 34.0% in the SPCBC group ($p < 0.0001$) (Fig. 1, Tab. III). Additionally, survival between LCBI and SPCBC groups did not differ significantly at any of those times (Tab. IV).

In a univariate analysis, age over 40 years, allogeneic HSCT, time to engraftment, acute GVHD grades III–IV, LCBI, and SPCBC, were risk factors for mortality. Conversely, gender, degree of HLA mismatch between donor and recipient, acute myeloid leukaemia, CMV reactivation or neutropenic fever were not found to significantly influence survival (Tab. V).

In the multivariable analysis of mortality, the variables such as age on admission over 40 years, type of HSCT, acute GVHD grades III and IV, time to engraftment over 15 days, and type of blood culture were integrated. After adjusting for other variables, both LCBI and SPCBC were still independent predictors of mortality (Fig. 2). Mortality was also independently influenced by age on admission over 40 years and presence of acute GvHD grades III and IV (Tab. VI).

Table II – Bacterial cultures within SPCBC and LCBI groups

Organism	Number of isolates [*n*]
LCBI	**38**
Escherichia coli	10
Klebsiella pneumoniae	8
Enterococcus faecium	5
Enterobacter cloacae	4
Pseudomonas aeruginosa	4
Enterococcus faecalis	2
Klebsiella oxytoca	2
Stenotrophomonas maltophila	1
Acinetobacter haemolyticus	1
Burkholderia cepacia	1
SPCBC	**33**
Staphylococcus epidermidis	21
Staphylococcus haemolyticus	8
Staphylococcus hominis	4
Total	**71**

LCBI – Laboratory-Confirmed Bloodstream Infection; SPCBC – Single Positive Commensal Blood Culture.

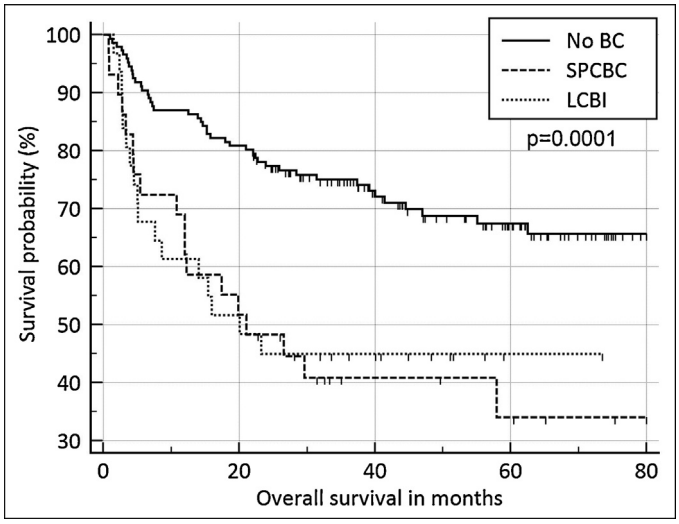

Fig. 1 – Mortality associated with positive blood cultures after HSCT

Discussion

The current definitions of LCBI and CLABSI downplay the meaning of single positive blood culture with bacteria regarded as common human commensals even in the presence of clinical symptoms of the disease [8, 9]. Our results show that in HSCT patients with a positive blood culture, even a single staphylococcal isolate (including *Staphylococcus epidermidis*) is associated with higher long-term mortality.

The common perception of this bacteria species relies on definition of LCBI – they are treated as contaminants unless two separate cultures are positive. This playing down of staphylococci is also present in analyses of infectious complications after HSCT – they do not include separate survival graphs for patients with coagulase negative staphylococci (CNS) although those bacteria constitute often more than 50% of infections in HSCT patients at some centres.

Is a positive staphylococcal blood culture a causative factor of increase in mortality or does increased susceptibility to this commensal reflect changes in patient subpopulation caused by general poorer clinical condition? We show that the risk of SPCBC per day of hospitalization is almost identical in allogeneic and autologous transplantations, and it remains an independent risk factor for lower survival in multivariate analysis. As there is new data that shows that the early use of antibiotics might lower the long-term survival of the patients after HSCT the findings of this work might also reflect the increased use of antibiotics in this group of patients [14]. The early SPCBC could be a trigger to the use of antibiotics with further changes to the bacterial flora of the recipient that could later lead to lower survival. As the short-term mortality and long-term survival after LCBI and SPCBC are similar, we have to look at the similarities between those cases that could explain those findings. The results of our work indicate that the SPCBC is not an indicator of status of the patients and very likely plays a prominent role in a cascade of factors leading to increased mortality among HSCT recipients.

One of the key factors in prevention of staphylococcal SPCBC is quality of CVC maintenance in HSCT patients – would it be possible to substantially improve survival after HSCT just by improving the prevention of CLABSI? We know that the CVC standards might still not be optimal in many HSCT centres and that the improvement of these standards is needed [15]. It would be very interesting to see if the improvement of CLABSI prevention leads to better long-term survival after HSCT.

There are several limitations to this study. Autologous and allogenic transplantations are analyzed together. Survival in both groups does differ significantly reflecting differences between those types of transplantations. However,

Table III – 100-day, 3-year and 5-year survival rates in patients with LCBI and SPCBC, and no BC

	No BC	LCBI	SPCBC	*p*-value
100-day survival rate	99.6%	83.9%	82.8%	0.0036
3-year survival rate	75.0%	44.9%	40.8%	0.0004
5-year survival rate	67.1%	44.9%	34.0%	<0.0001

LCBI – Laboratory-Confirmed Bloodstream Infection; SPCBC – Single Positive Commensal Blood Culture; No BC – patients without positive blood cultures.

Table IV – 100-day, 3-year and 5-year survival rates in patients after LCBI and SPCBC

	LCBI	SPCBC	*p*-value
100-day survival rate	83.9%	82.8%	0.8830
3-year survival rate	44.9%	40.8%	0.9026
5-year survival rate	44.9%	34.0%	0.7935

LCBI – Laboratory-Confirmed Bloodstream Infection; SPCBC – Single Positive Commensal Blood Culture.

Table V – Potential univariate predictors of mortality

Potential predictor	Died (%)	Survived (%)	HR (95% CI)	*p*-value
Age on admission greater than 40 years				
Under 40 years	31 (28.4)	78 (71.6)	1.00	0.0010
Over 40 years	49 (50.5)	48 (49.5)	2.08 (1.34–3.24)	
Gender				
Male	41 (36.6)	71 (63.4)	1.00	0.4367
Female	39 (41.9)	54 (58.1)	1.19 (0.77–1.85)	
Type of transplantation				
Autologous	15 (22.4)	52 (77.6)	1.00	0.0004
Allogeneic	65 (46.8)	74 (53.2)	2.63 (1.68–4.14)	
Underlying disease[a]				
Other than acute myeloid leukaemia	42 (30.2)	97 (69.8)	1.00	0.0639
Acute myeloid leukaemia	38 (56.7)	29 (43.3)	1.59 (0.98–2.61)	
HLA match[a]				
10 of 10	59 (46.5)	68 (53.5)	1.00	0.4272
9 of 10	9 (56.3)	7 (43.8)	1.32 (0.61–2.9)	
CMV reactivation[a]				
Absent	58 (46)	68 (54)	1.00	0.8721
Present	6 (46.2)	7 (53.8)	0.93 (0.39–2.22)	
Acute GvHD[a]				
GvHD 0-II	56 (43.8)	72 (56.2)	1.00	0.0211
GvHD III-IV	8 (72.7)	3 (27.3)	2.33 (0.82–6.66)	
Neutropenic fever				
Absent	45 (37.5)	75 (62.5)	1.00	0.8567
Present	35 (40.7)	51 (59.3)	1.04 (0.67–1.62)	
Time to engraftment				
Under 15 days	32 (30.2)	74 (69.8)	1.00	0.0027
Over 15 days	47 (49.0)	49 (51.0)	1.96 (1.26–3.07)	
Presence of a positive blood culture				
No	44 (30.1)	102 (69.2)	1.00	0.0001
Yes	35 (58.3)	25 (41.7)	2.64 (1.56–4.50)	
Type of blood culture				
No BC	45 (30.8)	101 (69.2)	1.00	
LCBI	17 (54.8)	14 (45.2)	2.52 (1.26–5.02)	0.0065
SPCBC	18 (62.1)	11 (37.9)	2.68 (1.34–5.36)	0.0016

[a] Adjusted for HSCT type.

the occurrence of blood stream infections is similar in both groups and almost identical when per diem rates are included. This suggests that the time of hospitalization might be the most important factor in patient population with central venous catheter inserted for the whole period of hospitalization. We feel that the data from autologous HSCT is an important addition to this study, putting into perspective data from allogenic HSCT. Moreover, the

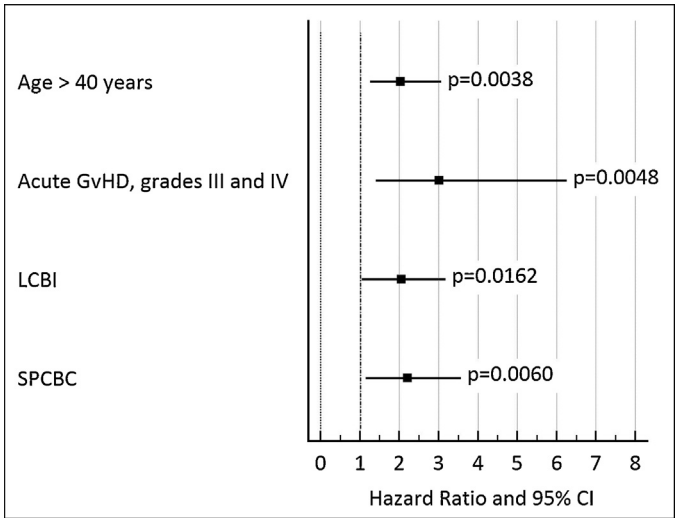

Fig. 2 – Independent factors of mortality (multivariate analysis). LCBI – Laboratory-Confirmed Bloodstream Infection; SPCBC – Single Positive Commensal Blood Culture

Table VI – Independent predictors of mortality (multivariate analysis)

Predictor	Hazard ratio (95% CI)	*p*-value
Age on admission over 40 years	2.04 (1.26–3.29)	0.0038
Allogeneic HSCT	1.41 (0.69–2.90)	0.3521
Acute GvHD, grades III and IV	3.01 (1.40–6.46)	0.0048
Time to engraftment over 15 days	1.27 (0.73–2.21)	0.3996
LCBI	2.05 (1.15–3.67)	0.0162
SPCBC	2.21 (1.26–3.87)	0.006

LCBI – Laboratory-Confirmed Bloodstream Infection; SPCBC – Single Positive Commensal Blood Culture.

multivariate analysis helps to differentiate the effect that allogenic or autologous HSCT has on long-term mortality from the effect SPCBC – and this part of analysis shows early SPCBC as an independent risk factor for mortality after HSCT. We were only able to analyze the aGvHD occurrence in the timeframe shortly after the transplantation and the study database was not designed to analyze causes of long-term non-transplantation related mortality in the groups (such as infection, GvHD, or recurrent and refractory disease). The knowledge of these factors could greatly improve our understanding of factors contributing to higher mortality after the SPCBC. It could be argued that SPCBC appears only in patients who are in worse general condition prior to transplantation and have reduced survival which is rather caused by underlying disease than SPCBC. However, even if this statement was true it would not explain why short-term and long-term mortality after SPCBC and LCBI is similar – where latter is caused by more virulent bacteria species. *Staphylococcus epidermidis* sepsis frequency seems to depend on common factors present in allo and auto HSCT setting, such as CVC presence, time of hospitalization and time of neutropenia.

Contradicting the general view of *Staphylococcus* spp. as relatively unimportant commensals and contaminants, we show that the short- and long-term mortality in patients who have at least one positive culture with this bacterium is similar to mortality among patients after sepsis with more virulent strains of bacteria. This raises a question if current LCBI definitions are appropriate for this patient population and how the early SPCBC contributes to short and long-term mortality after HSCT.

Authors' contributions/ Wkład autorów

ES – concept/desing, data analysis/interpretation, drafting article, data collection. KB – data analysis/interpretation, drafting article, statistics. WWJ – data analysis/interpretation, critical revision of article. TT, KH – data analysis/interpretation, critical revision of article, data collection. PR, MR, GB, MP, PB, GC, MT – data collection.

Conflict of interest/ Konflikt interesu

None declared.

Financial support/ Finansowanie

None declared.

Ethics/ Etyka

The work described in this article have 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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