Chapter 7

Storage time of platelet concentrates and all-cause bacteremia in hematological patients

Aukje L. Kreuger[1,2], Rutger A. Middelburg[1,2], Cock M.C. Bank[3], Erik A.M. Beckers[4], Adriaan J. van Gammeren[5], Anja Leyte[6], Jan M.M. Rondeel[7], Karen M.K. de Voogt[8], Floor Weerkamp[9], Jaap Jan Zwaginga[1, 10], Jean Louis H. Kerkhoffs[1,11], Johanna G. van der Bom [1,2]

[1] Center for Clinical Transfusion Research, Sanquin Research, Leiden.
[2] Dept. of Clinical Epidemiology, Leiden University Medical Center, Leiden. [3]Admiraal de Ruyter Hospital, Goes.
[4]Maastricht University Medical Center, Maastricht.
[5]Amphia Hospital, Breda.
[6]OLVG Hospital, Amsterdam.
[7]Isala Klinieken, Zwolle.
[8]University Medical Center Utrecht, Utrecht.
[9]Maasstad Hospital, Rotterdam.
[10]Dept. of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden.
[11]Haga Teaching Hospital, Den Haag.

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Abstract

Background

Extension of storage time of platelet concentrates may result in an increased risk of bacteremia, directly via transfusion of contaminated products or indirectly via transfusion related immunomodulation. We aimed to quantify the association of storage time of platelet concentrates and all-cause bacteremia in hematological patients.

Design and methods

We established a cohort of hematological patients who received a platelet transfusion between 2005 and 2015. Cases were defined as patients with a bacteremia the day after transfusion, and matched to as many controls as possible. A conditional logistic regression was performed, stratified by storage medium.

Results

Among 3,514 patients receiving 36,032 platelet concentrates stored in plasma, 613 cases of bacteremia were found. The relative risk of all-cause bacteremia the day after transfusion was 0.80 (CI 0.58-1.12) for platelet concentrates stored 3-4 days and 0.67 (CI 0.49-0.92) for ≥ 5 days, compared to ≤2 days. Among 1,527 patients receiving 11,822 platelet concentrates stored in platelet additive solution (PAS), 182 cases of bacteremia were found. The relative risk of all-cause bacteremia was 1.14 (CI 0.70-1.84) for platelet concentrates stored 3-4 days and 1.19 (95% CI 0.70-2.01) for ≥ 5 days, compared to ≤2 days.

Conclusion

Storage time of platelet concentrates was not associated with increased occurrence of all-cause bacteremia the day after transfusion. If anything, fewer bacteremia occurred with increasing storage time of platelet concentrates in plasma. These bacteremias are not directly caused by transfusion of a contaminated product and the underlying mechanism warrants further research.

Introduction

Transfusion of platelets is an important aspect of supportive care in the treatment of patients with hematological malignancies, to prevent or treat bleeding complications during periods of severe thrombocytopenia.[1,2] The concurrent neutropenia predisposes these patients to infectious complications.[3]

Transfusions can directly cause bacterial infections via transmission of bacteria through contaminated products. In particular platelet concentrates may carry this risk, as these are stored at room temperature, allowing bacterial proliferation. This is clearly illustrated by several case reports of severe bacterial sepsis after transfusion of contaminated platelet concentrates.[4-7] In an attempt to reduce this risk, storage time is limited to 3.5 days in Japan and to four and five days in the USA and Germany. [8-11] A large trial in the USA, which aimed to investigate the safety of seven days storage with the implementation of early testing, was terminated early due to concerns about the residual risk of transfusion of a contaminated platelet concentrate.[12] However, storage up to seven days in combination with bacterial screening is allowed in, among others, Spain, the United Kingdom, Sweden and the Netherlands.[11] Bacterial screening does not eliminate the risk of septic reactions completely as false negative results occur. In most studies, septic reactions were associated with platelet concentrates stored for four to six days.[5,13-16]

The risk of infections does not solely depend on sterility of the platelet concentrate. Besides direct transmission of infections with a contaminated product, it has been speculated that platelets itself play a role in the immune response and that transfusions could modulate this response.[17-19] Immunosuppressive effects of a transfusion could result in an increased incidence of all-cause bacteremias.

The aim of this study was therefore to quantify the association of storage time of platelet concentrates screened for bacterial contamination and stored for up to seven days in plasma or platelet additive solution (PAS) with all-cause bacteremia in a large cohort of hematological patients.

Methods

Design and population

We performed a case control study, nested in a cohort of recipients of platelet transfusions from nine hospitals in the Netherlands, three university and six general hospitals (supplemental material, table S1). The study population consisted of all patients with a hematological malignancy or aplastic anemia who had received at least one platelet transfusion between January 2005 and December 2015. The study period varied between participating hospitals (supplemental material). Patients were selected based on DBC code (Diagnosis treatment combination). Selected diagnoses were leukemia, lymphoma, myeloma, and aplastic anemia (selected codes are depicted in the supplemental material). We excluded patients younger than one year, as transfusion policies in neonates differ from those of the general population. The study protocol was approved by the Medical Ethical Committee of each participating hospital.

Platelet products

Buffy-coats were produced from whole blood after overnight hold and leuko- and plasma-reduced. Buffy-coats of five donors were pooled and re-suspended in plasma or platelet additive solution (PAS), with 25 mL of plasma per donor to a final volume of 300-350ml.[1,20] The geographic location of the hospital determined which storage medium was used.[21] Transfusion of platelet concentrates stored in storage medium not normally used in that hospital were assumed to be given for exceptional indications and therefore excluded from all analyses. PAS-B (T-sol, Baxter) was used as storage medium through 2012, with PAS-C (Intersol, Fenwal, Inc) being used as of January 2013. Maximum storage time for platelets stored in PAS-B was five days. Platelets stored in PAS-C or plasma could be stored for a maximum of seven days. Hyper-concentrated products and platelet concentrates collected via apheresis were excluded from all analyses as these were only used for specific indications.[1] All platelet concentrates were sampled immediately after preparation and screened for bacterial contamination with the BacT/Alert system consisting of an aeroob and anaeroob culture bottle, inoculated with 7.5ml each, and released on a 'negative-to-date' basis.[1,20]

Variables

Characteristics of blood products were extracted from the national blood bank system. Recorded variables were donation date, storage medium, ABO and RhD blood group, and product type. Storage time was counted in days from the day of donation (day 0) up to and including the day of transfusion. Storage time was categorized into three groups: ≤2 days, 3-4 days, ≥5 days. Product identification numbers were used to link this information to clinical data. Patient characteristics were extracted from the electronic health care system of the participating hospitals. Recorded variables were age, gender, AB0 and RhD blood group, positive blood cultures, transfusions of platelets, and all DBC codes.

Cases

Cases were defined as patients who received at least one platelet transfusion and had a bacteremia the day after transfusion. In order to select these cases, we linked clinical data, including all positive blood cultures, to transfusion data using the patient identification numbers. If a patient received multiple transfusions of different storage time categories on the same day, these transfusion-days were excluded from all analyses. A bacteremia was defined as a positive blood culture. Blood cultures were not standardly performed the day after transfusions, but only taken on indication or scheduled in certain treatment protocols. One patient could develop multiple bacteremias. A period of fourteen days between two positive blood cultures, regardless of negative cultures in between, was required to ensure two bacteremia episodes were unrelated.

Controls

Cases were matched to as many control transfusion-days as possible. If a case received platelet transfusions on several days, all transfusions which were not followed by a positive blood culture could be included as control for this or other cases (i.e. one patient could be included as case as well as control). Matching factors were hospital, day of the week, number of transfusions on a single day, AB0 blood group, and storage medium. To account for this matching, a conditional logistic regression was performed using the youngest storage time category as a control for the exposure and adjusted for the matching factors. As the controls derive from the entire cohort, the odds ratios could be interpreted as relative risks.[22,23]

Additional analyses

We performed five additional analyses to explore the impact of possible sources of bias and effect modification.

First, we performed a subgroup analysis among patients with the highest risk of infections. Here we limited the analysis to intensively treated hematological patients by selecting patients with a diagnosis of acute leukemia, or high grade non-Hodgkin lymphoma.

Second, we investigated the association of storage time in different generations of additive solutions, i.e. PAS-B and PAS-C.

Third, we investigated the association of different generations of platelet additive solutions with bacteremia, stratified by storage time category. This was possible as prior to 2013 the Dutch blood supply organization used exclusively PAS-B as an additive solution, whereas after 2013 exclusively PAS-C was used. Therefore we used calendar time as instrumental variable in this analysis.

Fourth, we used a negative control to explore any residual confounding.[24] Therefore, we selected cases with bacteremia the day before transfusion.

Fifth, to explore any immune-modulatory effects of storage, we investigated the association of bacteremia with storage time of platelet concentrates transfused two or three days before. Patients who received transfusions on several days before bacteremia were excluded from this analysis (i.e. in the analysis regarding transfusions given three days before bacteremia, we excluded patients who also received a transfusion one or two days before bacteremia).

Results

Study population

The total cohort consisted of 5,008 patients who received 47,854 platelet transfusions on 43,450 days (figure 1 supplemental material). Patients were on average 56.5 years old (SD 17.8), 60.8% of patients were male, and 43.8% were diagnosed with acute leukemia. On 62.9% of analyzed days a plasma stored platelet concentrate was given to a patient with acute leukemia, which was on 56.3% of days for platelets stored in PAS (table 1). Patient received one transfusion (range 1 to 10 transfusions) on 91.4% of the analyzed days. 660 patients developed bacteremia the day after transfusion, for a total of 795 transfusion-days, with a median of 1 (range 1 to 6) bacteremia per patient.

Median storage time of platelet concentrates stored in plasma was 5 days (interquartile range [IQR]: 4 to 6 days) and 4 days (IQR: 3 to 5 days) for platelet

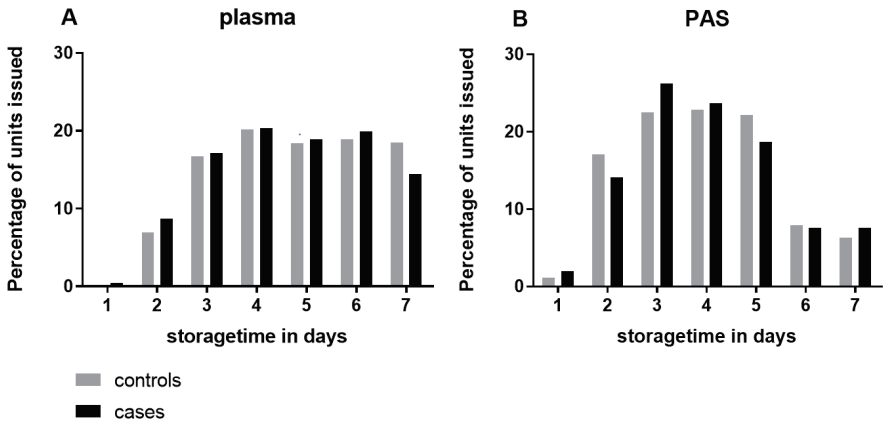
concentrates stored in PAS. Median storage time was 3 days (IQR: 3 to 4 days) for platelet concentrates stored in PAS-B and 5 days (IQR: 3 to 6 days) for platelet concentrates stored in PAS-C. The distribution of storage time for cases and controls, stratified by storage medium, is shown in figure 1 and in the supplemental material for the different generations of PAS.

Table 1. Baseline characteristics patients

Plasma	**Total**	**≤2 days**	**3-4 days**	**≥5 days**
Transfusion days	32,734	2,390 (7.3)	12,100 (37.0)	18,244 (55.7)
Patients*	3,514	1,240	2,671	3,030
Age in years, mean (SD)	52.8 (17.6)	52.3 (17.3)	52.6 (17.5)	53.1 (18.0)
Male sex (%)	20,856 (63.7)	1,540 (64.4)	7,672 (63.4)	11,644 (63.8)
Number of transfusions per day, median (range)	1 (1-10)	1 (1-6)	1 (1-10)	1 (1-8)
Diagnosis				
-Acute leukemia	20,575 (62.9)	1,409 (58.9)	7,596 (62.8)	11,570 (63.4)
-Lymphoma	4,955 (15.1)	413 (17.3)	1,802 (14.9)	2,740 (15.0)
-Myeloma	2,275 (6.9)	160 (6.7)	871 (7.2)	1,244 (6.8)
-Chronic leukemia	2,289 (7.0)	188 (7.9)	846 (7.0)	1,255 (6.9)
-Aplastic anemia and other	2,640 (8.1)	220 (9.2)	985 (8.1)	1,435 (7,9)
PAS	**Total**	**≤2 days**	**3-4 days**	**≥5 days**
Transfusion days	10,716	1,994 (18.6)	4,840 (45.2)	3,882 (36.2)
Patients*	1,527	798	1,180	1,051
Age in years, mean (SD)	59.4 (15.0)	58.6 (14.7)	59.5 (15.1)	59.9 (15.0)
Male sex	6,633 (61.9)	1,174 (58.9)	3,000 (62.0)	2,459 (63.3)
Number of transfusions per day, median (range)	1 (1-5)	1 (1-5)	1 (1-5)	1 (1-4)
Diagnosis				
-Acute leukemia	6,033 (56.3)	1,053 (52.8)	2,692 (55.6)	2,288 (58.9)
-Lymphoma	2,192 (20.5)	457 (22.9)	1,003 (20.7)	732 (18.9)
-Myeloma	1,258 (11.7)	271 (13.6)	579 (12.0)	408 (10.5)
-Chronic leukemia	577 (5.4)	133 (6.7)	260 (5.4)	184 (4.7)
-Aplastic anemia and other	656 (6.1)	80 (4.0)	306 (6.3)	270 (7.0)

Numbers represent number of transfusion days (percentages) unless otherwise specified.
** Total numbers reflect unique patients. Numbers in subgroups don't add up till total numbers, since one patient could contribute transfusion-days to several storage time categories.*

Figure 1. Storage time of platelet concentrates for cases and controls

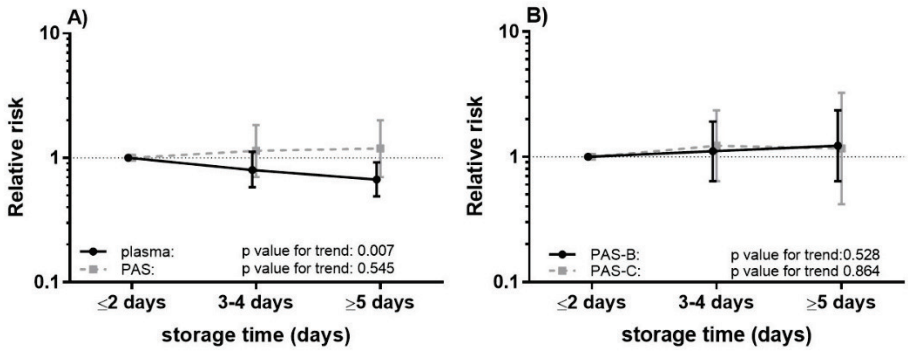


Panel A) storage time of platelet concentrates stored in plasma
Panel B) storage time of platelet concentrates stored in PAS

Platelets in plasma

Among 3,514 patients receiving 36,032 plasma-stored platelet concentrates on 32,734 different days, 613 cases of bacteremia were detected the day after transfusion. In 56 cases the patient had received a platelet concentrate stored for ≤2 days (incidence 2.34/100 transfusion-days; 95% confidence interval (CI): 1.76 to 3.04), in 232 cases a platelet concentrate stored for 3-4 days (incidence 1.91/100 transfusion-days; CI: 1.68 to 2.18) and in 325 cases a concentrate stored for ≥5 days (incidence 1.78/100 transfusion-days; CI: 1.59 to 1.99) (table 1). The adjusted relative risk of all-cause bacteremia was 0.80 (CI: 0.58 to 1.12) after transfusion of a platelet concentrate stored for 3-4 days and 0.67 (CI: 0.49 to 0.92) after transfusion of a concentrate stored for ≥ 5 days, compared to transfusion of concentrates stored for ≤ 2 days, p value for trend: 0.007 (figure 2, crude analysis supplemental material).

Figure 2. Storage time and risk of all-cause bacteremia



Relative risk of all-cause bacteremia one day after transfusion of platelet concentrates stored 3-4 days or ≥5 days, compared to platelet concentrates stored ≤2 days, stratified on storage medium. Relative risks are adjusted for number of transfusions, ABO blood group, day of the week, and hospital. Estimates for PAS stored platelet concentrates are also adjusted for generation of PAS.
Panel A) platelet concentrates stored in plasma or PAS
Panel B) platelet concentrates stored in PAS-B or PAS-C

Platelets in PAS

Among 1,527 patients receiving 11,822 PAS-stored platelet concentrates on 10,716 different days, 182 cases of bacteremia were detected the day after transfusion. In 31 cases the patient had received a platelet concentrate stored for ≤2 days (incidence 1.55/100 transfusion-days; CI: 1.06 to 2.20), in 90 cases a concentrate stored for 3-4 days (incidence 1.86/100 transfusion-days; CI: 1.50 to 2.29) and in 61 cases a concentrate stored for ≥5 days (incidence 1.57/100 transfusion-days; CI: 1.20 to 2.02) (table 1).The adjusted relative risk for developing a bacteremia was 1.14 (CI: 0.70 to 1.84) after transfusion of a platelet concentrate stored for 3-4 days and 1.19 (CI: 0.70 to 2.01) after transfusion of a concentrate stored for ≥5 days, p value for trend 0.545 (figure 2, crude analysis supplemental material table S3).

Additional analyses

For the first additional analysis only intensively treated patients were selected. In this subgroup of 333 cases receiving plasma-stored and 121 cases receiving PAS-stored platelet concentrates, results were similar to the entire cohort (supplemental material).

Second, subgroup analyses were performed for different generations of additive solutions. Storage time of platelet concentrates stored in PAS-B or PAS C was not associated with all-cause bacteremia (figure 2).

Third, the generation of additive solution was not associated with all-cause bacteremia (RR PAS-C versus PAS-B: 1.10, CI: 0.75 to 1.62)(table 2).

Fourth, as a negative control, we selected cases the day before transfusion. In both storage media, storage time was not associated with the risk of all-cause bacteremia the day before transfusion (supplemental material).

Finally, we re-performed our analysis with an increased length of follow up. Storage time of platelet concentrates was not associated with all-cause bacteremia two and three days after transfusion (supplemental material).

Table 2. Generation of additive solution and risk of bacteremia

	Overall	≤2 days	3-4 days	5 days
Crude	1.11 (0.77-1.60)	0.90 (0.34-2.35)	1.21 (0.76-1.93)	1.00 (0.48-2.10)
Adjusted	1.10 (0.75-1.62)	1.02 (0.38-2.73)	1.20 (0.73-1.97)	0.93 (0.42-2.07)

Relative risk of all-cause bacteremia one day after transfusion of a platelet concentrate stored in PAS-C compared to PAS-B, stratified on storage time. The risk ratios are adjusted for number transfusions, AB0 blood group, day of the week, hospital, and storagetime.

Discussion

Transfusion of platelet concentrates stored ≥5 days in plasma, with 100% bacterial screening, was associated with a decreased risk of all-cause bacteremia the day after transfusion in patients with hematological malignancies. Storage time of platelet concentrates stored in PAS was not associated with all-cause bacteremia. For both storage media, storage time was not associated with all-cause bacteremia two or three days after transfusion. It is not known what role immunomodulation plays in producing the data we report.

Transfusion associated sepsis is often under-recognized and under-reported.[25] To capture all bacteremias, potentially related to a transfusion, we included all bacteremias the day after transfusion. We did not differentiate between various

potential causes of bacteremia and platelet concentrates were not re-cultured at time of transfusion. The incidences of bacteremia are higher than the incidence of infections exclusively caused by transfusion of a contaminated platelet concentrate. Active surveillance revealed an incidence of transfusion-transmitted infections ranging from 389 till 485 per million transfusions.[13,25] In our study the incidence of bacteremia was approximately 35 times higher, which would indicate that 14-17 of the 613 bacteremias after transfusion of a plasma stored platelet concentrate and 5 of the 182 bacteremias after transfusion of a PAS stored platelets are directly caused by contamination of the transfused products. This misclassification is not related to storage time and could therefore have biased the results towards the null (i.e. no association). The older storage time category contained relatively more transfusion days of patients with acute leukemia. Since these patients have the highest risk of infections, this could bias the results towards an increased risk of older platelets. However, we still found a lower risk of all-cause bacteremia after transfusion of older platelet concentrates stored in plasma. It is therefore exceedingly unlikely that the true effect is in the opposite direction. The lack of an association in the negative control supports our findings.

The assumed increased risk of bacteremia is one of the main arguments for limiting the shelf life of platelet concentrates.[26,27] The results of our study pertain all-cause bacteremia, which emphasizes all bacteremias and not exclusively transfusion-transmitted bacteremia, but based on these results, this argument seems at least unjustified regarding all-cause bacteremia for platelet concentrates stored in plasma when 100% bacterial screening is employed.

A limitation of this study, pertaining only to the results regarding PAS-stored platelet concentrates, is the limited number of cases, as only a subset of the hospitals used PAS stored platelet concentrates. For the majority of the study period, PAS-B stored platelet concentrates, which had a maximal storage time of only five days, were used. A limited range in possible storage time will automatically limit the differences. In several studies an association between platelet transfusions and risk of all-cause infection has been reported.[28-30] However, confounding by indication could be a potential explanation for these findings, since patients receiving platelet transfusions are at an inherently different risk of infection than those not receiving platelet transfusions. We here investigated differences in storage time, since platelet products are released on a first-in-first-out basis, without consideration of the patients' prognoses. During storage the risk of transfusion-transmitted infections increases [5,12,31] The effect of storage time on all-cause infections is less

studied and prior studies reported conflicted results.[32] One study reported an increased incidence of bacterial sepsis with each day increase of storage time in critically ill trauma patients.[33] Another study found no association between storage time of a single platelet concentrate and postoperative infections after cardiac surgery.[34] In contrast to these studies, we found a lower risk of all-cause bacteremia after transfusion of old platelet concentrates stored in plasma. This difference could possibly be explained by differences in platelet concentrate characteristics. In our study, platelet concentrates were buffy-coat derived and maximally stored for seven days, whereas in both other studies platelet concentrates were collected via apheresis and maximum storage time was limited to five days.

A higher incidence of contamination in fresh products could explain the lower risk of all-cause bacteremia after transfusion of longer stored platelet concentrates. With each day of storage the BacT/Alert will detect more contaminated products. However, the total incidence of positive screening results is only around 0.37% and this could not explain the total effect.[20] Moreover, platelet concentrates are cultured until the end of shelf-life. Approximately 80-100 units per year are transfused before the initial BacT/Alert turns out positive. Look-back procedures have shown that these only rarely lead to clinically significant infections.[35]

Another explanation for our results could be an immunomodulatory effect of platelet transfusions. Transfusion Related Immunomodulation (TRIM) has been studied in relation to red cell transfusions.[36] To which extend transfusion of platelets also modulate the immune response is less clear.[37] It has been shown *in vitro*, that levels of platelet-derived-growth factor and sCD40L (platelet activation factor) increase during storage.[38] In contrast, in mice, it has been suggested that fresh platelets have an immunosuppressive effect due to loss of the expression of MHC class I molecules during storage.[39] This would be in line with the increased incidence of all-cause bacteremia after transfusion of fresh platelet concentrates. We hypothesized that immune-modulatory effects of storage time of platelet transfusions probably last longer than one day. We therefore increased the time between transfusion and detection of bacteremia. However, we did not find an association between storage time and all-cause bacteremia after two or three days.

The lower risk of bacteremia after transfusion of older platelet concentrates stored in plasma was not observed for platelet concentrates stored in PAS. This could suggest that storage medium modifies the effect of storage time. It is known that not all bacteria are able to proliferate in platelet concentrates and some bacteria even die during storage, a process referred to as auto-sterilization.[40,41] This may be

more pronounced in platelet concentrates stored in plasma since plasma contains a mix of bactericidal proteins and enzymes.

Our study did not allow the comparison of risk of bacteremia with respect to storage medium itself. The lower incidences of bacteremia after transfusion of PAS stored platelet concentrates may suggest a beneficial effect of PAS. However, although storage medium was solely determined by geographic location of the hospital, the included type of hospitals and thereby also the type of patients differed substantially between the different storage media. These substantial differences hamper a direct comparison of storage media and we did not attempt to adjust for this confounding.

In conclusion, in patients with hematological malignancies, storage time of plasma-stored platelet concentrates was associated with a decreased occurrence of all-cause bacteremia the day after transfusion, whereas storage time was not associated with the incidence of all-cause bacteremia the day after transfusion of PAS-stored platelets.

Supplemental material

Available at http://onlinelibrary.wiley.com/doi/10.1111/trf.14194/abstract

Table S1. Participating hospitals
Table S2. Selected DBC codes for hematological malignancies
Table S3. Storage time and risk of all-cause bacteremia
Table S4. Storage time and risk of all-cause bacteremia one day after transfusion in most intensively treated patients
Figure S1. Flow chart of data handling
Figure S2. Storage time of platelet concentrate stored in PAS –B and PAS-C for cases and controls
Figure S3. Storage time and risk of all-cause bacteremia the day before transfusion
Figure S4. Storage time and risk of all-cause bacteremia 2 or 3 days after transfusion

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