Chapter 9

Storage medium of platelet transfusions and the risk of transfusion transmitted bacterial infections

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Abstract

Transfusion transmitted bacterial infections (TTBI) are among the most concerning risks of transfusion of platelet concentrates. Storage medium influences bacterial growth dynamics and thereby the sensitivity of screening tests for bacterial contamination. The aim of this study was to quantify the association of storage media with the incidence of TTBI after transfusion of platelet concentrates. In the Netherlands, the choice of storage medium is determined solely by geographic location of the hospital. We compared types of storage medium of all reported cases of TTBI following transfusion of a platelet concentrate with types of storage medium of all produced platelet concentrates in the Netherlands from 2003 to 2014. Fourteen cases of TTBI were reported, of which 57.1% received a platelet concentrate stored in platelet additive solution (PAS) and 42.9% a platelet concentrate stored in plasma. Of all produced platelet concentrates 22.3% were stored in PAS and 77.7% in plasma. The relative risk of TTBI after transfusion of a PAS stored platelet concentrate was 4.63 (95% confidence interval (CI) 1.4 to 16.2) compared to transfusion of a plasma stored platelet concentrate. The incidence of TTBI was 22.2 per million (CI 12.1 to 37.2 per million) transfused buffy coat platelet concentrates.

Introduction

Transfusion transmitted bacterial infections (TTBI) are one of the leading causes of mortality associated with blood transfusion.[1] Risk of TTBI is particularly associated with transfusion of platelet concentrates, as these are stored at room temperature, allowing for proliferation of bacteria.

In many countries, platelet concentrates are screened for bacterial contamination, using the BacT/Alert culture system, and released on a 'negative-to-date' basis.[2] Despite preventive efforts, still a significant number of TTBIs are reported every year. With complete bacterial screening, the incidence of TTBI was 7.14 per million platelet transfusions in Germany between 1997 and 2007, and 9.14 per million in the USA (2007-2011).[3,4] Approximately 300,000 platelet concentrates are transfused yearly in the United Kingdom and in 2015 the first case since 2009 was reported.[5] In the absence of bacterial screening, the incidence of TTBI was 26.5 per million In France (2009-2011).[6]

Sensitivity of the screening method is influenced by variability in the inoculum and kinetics of bacterial growth.[7] Bacteria have been shown to be present in higher concentrations, making them more likely to be detected by culture methods, in apheresis and buffy coat derived platelet concentrates stored in platelet additive solution (PAS), as compared to those stored in plasma.[8-10]

Interestingly, for some products yielding a positive BacT/Alert screen, a subsequent resampling of the stored platelet concentrate results in a negative culture.[11] Apparently not all bacteria are able to proliferate in a platelet concentrate. It has been suggested that complement and antibodies can eliminate bacteria and sterilize the blood product. This process of auto-sterilisation is probably more pronounced in platelet concentrates stored in plasma than in those stored in PAS.[12]

It is not known how these different effects of storage media influence the total risk of TTBI. The aim of this study was to quantify the association of storage medium with the incidence of TTBI after transfusion of a platelet concentrate.

Methods

We performed a nested case control study to assess the effect of storage of platelet concentrates in plasma or PAS on the risk of TTBI. We included all cases of TTBI in which a platelet transfusion was involved that had been reported to the national hemovigilance organization 'Transfusion and Transplantation Reactions in Patients'

(TRIP) between 2003 to 2014. TRIP is the Dutch competent authority to which all transfusion reactions must be reported. Product identification numbers of the involved products were used to extract information about storage media and production method from the blood bank system. We excluded cases of TTBI that occurred after transfusion of platelet concentrates collected by apheresis for the main analysis, because these are used for specific indications and mostly stored in plasma.

TTBI was defined as clinical features of bacteremia or sepsis during or after transfusion, with a relevant positive blood culture in the patient and assessed with a high level of imputability (definite or probable) to the transfused product. Imputability of all cases of post-transfusion sepsis was assessed by an expert panel. Since 2011 the expert panel has additionally judged whether the bacterial culture findings support a formal classification of the case as TTBI. Severity of transfusion reactions was scored on a scale from 0 to 4, with 0 indicating 'no morbidity' and 4 indicating 'mortality'.[13]

Platelet concentrates were prepared from buffy-coats of five donors, leukoreduced, and resuspended in plasma, or platelet additive solution (PAS), with 25 ml of plasma left per donor. PAS-B (T-sol, Baxter) was used through 2013, with PAS-C (Intersol, Fenwal, Inc) being used since. The diversion pouch was introduced universally in July 2004.[14] Throughout the entire study period, a standardized skin disinfection method was used and all platelet concentrates were screened for bacterial contamination with the BacT/Alert system (bioMérieux), according to a standardized protocol.

For the incidence of TTBI the number of all platelet concentrates produced in the Netherlands between 2003 and 2014 was used as the denominator. The storage medium of platelet concentrates involved in a TTBI was compared to storage medium of all produced platelet concentrates. Production data according to storage medium were available only for the period 2006-2014. The ratio of used storage media was stable over this period and could therefore be extrapolated back to 2003 (supplemental material). The type of storage medium of platelet concentrates is only determined by the geographical location of the hospital. Therefore location of the hospital where the case of TTBI arises behaves as an instrumental variable in this analysis and it is expected that all potential confounders are randomly distributed.[15] To assess this assumption we explored the distribution of storage medium among hospitals licensed for stem cell transplantations and we compared the incidences of transfusion reactions related to red blood cell transfusions between the regions. We performed two sensitivity analyses. First, we included apheresis products in our

analysis. Second, we excluded all cases before July 1st 2004, when use of the diversion pouch was introduced in all production centres.

Results and discussion

Between 2003 and 2014 fourteen cases of TTBI were reported to TRIP. Table 1 provides the characteristics of all these cases. One case was of minor severity (grade 1), ten cases were moderate to serious (grade 2), one was directly life-threatening (grade 3), and one was fatal (grade 4). Twelve patients had a hematological malignancy, one patients had a solid tumour (prostate carcinoma) and for one patient the indication for transfusion was stated to be thrombocytopenia without further reported diagnosis. Both cases in 2003 were related to Bacillus Cereus. The bacterial strains differed in genotype, so it seemed unlikely that both platelet concentrates were contaminated by a common source.[16]

During the study period 631,347 pooled buffy coat platelet concentrates were produced. The incidence of TTBI was 22.2 per million (95% confidence interval (CI) 12.1 to 37.2 per million) buffy coat platelet concentrates. This incidence is relatively high compared to other countries, which is probably a reflection of the accuracy of the Dutch hemovigilance system.[17]

Eight patients (57.1%) with TTBI received a PAS stored platelet concentrate (seven PAS-B, one PAS-C) and six patients (42.9%) received a platelet concentrate stored in plasma. Of all produced platelet concentrates, 22.3% were stored in PAS, and 77.7% in plasma. Transfusion of PAS stored platelet concentrates was associated with a relative risk of TTBI of 4.63 (95% CI 1.4 to 16.2) compared to plasma stored platelet concentrates. Including the platelet concentrates collected via apheresis showed similar results (RR 5.01; CI 1.66 to 15.83). Exclusion of the period before universal use of the diversion pouch yields a relative risk of 3.48 (CI 0.93 to 13.01).

Table 1. All cases of TTBI reported to TRIP between 2003 and 2014

Case	Year	Age in years	Diagnosis	Severity*	Bacteria	Storage medium
1	2003	18	Acute myeloid leukemia	2	Bacillus Cereus	PAS-B
2	2003	57	Chronic myeloid leukemia	N/A†	Bacillus Cereus	PAS-B
3	2004	28	N/A†	2	Bacillus Cereus	PAS-B
4	2005	33	Acute myeloid leukemia	2	Hemolytic streptococci group G	Plasma
5	2005	58	Mantle cell lymphoma	2	Bacillus Cereus	PAS-B
6	2005	46	Aplastic anemia	3	Staphylococcus aureus	PAS-B
7	2005	58	Non Hodgkin lymphoma	2	Hemolytic streptococci group G	Plasma
8	2008	53	Acute myeloid leukemia	2	Coagulase negative staphylococci	Plasma
9	2010	72	Prostate carcinoma	1	Coagulase negative staphylococci	PAS-B
10	2010	39	Acute myeloid leukemia	2	Streptococcus dysgalactiae	PAS-B
11	2011	59	Acute myeloid leukemia	2	Salmonella group B	Plasma
12	2012	75	Non Hodgkin lymphoma	2	Hemolytic streptococci group C	Plasma
13	2013	62	Chronic lymphoid leukemia	2	Coagulase negative staphylococci	PAS-C
14	2014	60	Multiple myeloma	4	Staphylococcus aureus	Plasma

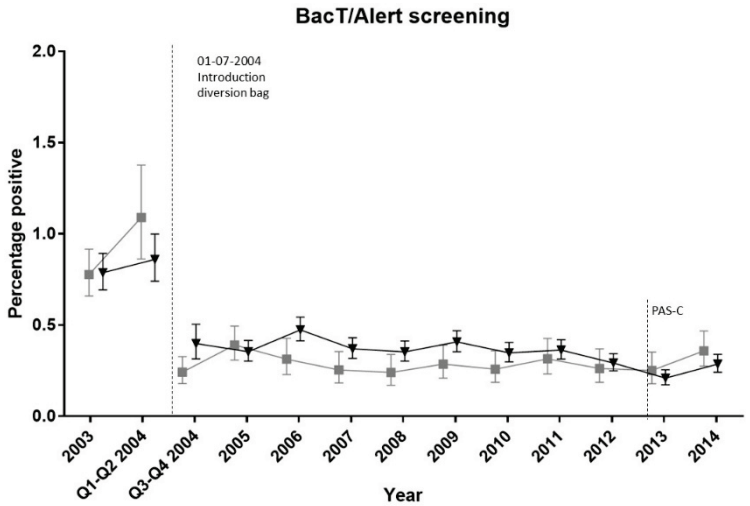
** Severity of transfusion reaction. Grade 1: minor morbidity, not life-threatening; grade 2: Moderate to serious morbidity, may or may not be life-threatening; or leading to hospitalisation or prolongation of illness; or associated with chronic disability or incapacity; grade 3: serious morbidity, directly life-threatening; grade 4: mortality following transfusion reaction.*

†N/A, Not available, information was not reported to TRIP.

The increased risk of TTBI after transfusion of PAS stored platelet concentrates could be explained by auto-sterilisation of plasma stored platelet concentrates, which potentially inhibits a high bacterial load in a contaminated product. The aforementioned *in vitro* studies showed differences in growth characteristics of some bacterial strains suggesting improved sensitivity of bacterial screening of platelet concentrates stored in PAS-C of PAS-E. However, as shown in figure 1, the frequency of confirmed positive results was higher for platelet concentrates stored in plasma compared to those stored in PAS-B. This is in line with the results of a

previous study which compared the screening results of all platelet concentrates in 2002 and 2003.[18] With our data, it was not feasible to compare the different generations of PAS, since PAS-C has only been in use for two years, during which only one case of TTBI related to PAS-C has been reported.

Figure 1. Percentage of confirmed positive results for all screened platelet concentrates screened by storage medium



Confirmed positive means a microorganism could be isolated from the positive bottle.[14] The diversion pouch has bene universally used since 1st July 2004. PAS-C has been in use since 1 January 2013.

This is the first clinical study investigating the association of storage medium of platelet concentrates with TTBI. Storage media differs among countries and several generations of additive solutions are used.[19] Incidences of TTBI could not be compared between countries, due to large differences in hemovigilance.[17]

In the Netherlands the choice of storage medium is determined solely by location of the hospital. Since it is likely that characteristics of patients receiving platelet concentrates are similar in different regions of the Netherlands, we expect that these are also equally distributed among storage media. Because most cases were diagnosed with hematological malignancies, we performed an additional check, selecting only those hospitals licensed for autologous or allogeneic stem cell transplantations. Among these hospitals, 20.4% of platelet concentrates were stored in PAS, which is comparable to the 22.3% observed for all hospitals. This reaffirms our assumption that patient characteristics are similar among the different

regions. Furthermore, differences in vigilance in reporting of TTBI could confound the results. The hospitals in which PAS stored platelet products are used reported 28.1% of TTBIs related to red blood cell products, whereas these hospitals transfused 22.6% of all red blood cell products (RR 1,34 (95% CI: 0,87-2,08)). This seems to indicate that differences in reporting behaviour cannot explain the observed strong association.

A limitation of this approach is that platelet concentrates in PAS and plasma were produced at different blood bank locations. Differences between these locations could theoretically also have affected the risk of TTBI. However, it seems unlikely that this could fully explain the observed strong association of storage medium with risk of TTBI.

To conclude, transfusion of PAS stored platelet concentrates is associated with a four-fold increased incidence of TTBI, compared to plasma stored platelet concentrates.

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Supplemental material

Available at http://onlinelibrary.wiley.com/doi/10.1111/trf.13969/abstract

Table S1. Distribution of storage medium over the years

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