

Blood Product Supply in Germany: The Impact of Apheresis and Pooled Platelet Concentrates

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Keywords

Antigen-matched platelets · Apheresis platelets · Donor pool · Pooled platelets · Red blood cell concentrates

Summary

Background: In Germany, about 60% of all produced platelet concentrates (PCs) are apheresis PCs (APCs). Ongoing discussions on APC reimbursement and costs might lead to a potential shift in pooled PC (PPC)/APC production. Objective of this analysis was to build a comprehensive model from the societal perspective to evaluate consequences associated with shifts in platelet supply and demand. **Methods:** Literature search, desktop researches on platelet supply and demand. Model calculations, time horizon one year: model input from the Paul-Ehrlich-Institute, data 2013. Base case: 19.2% of annual whole blood donations (WBDs) were used for production of 38.5% PPCs, decay of 46,218 PCs (8.0%). Scenarios calculated: variation in PPC proportion of 10–100%. **Results:** Base case: during PPC production 41,957–83,913 red blood cell concentrates (RBCCs) are estimated to be lost, which corresponds to 1–2% of annual RBCCs in Germany. Scenarios were calculated for a production of 60–100% PPCs: loss is estimated to be 1.5–5.0% of annual RBCCs (65,430–218,099), decay 54,189–69,022 PCs (9.4–12.0%). **Conclusion:** Production of different blood components is interlinked and sensitive to unidimensional decisions. Increasing PPC proportion has negative impact on the RBCC production and on the antigen-matched APC donor pool. Completion of the model calculations to predict the optimal PPC/APC proportion would require evidence on the number of refractory patients, donor pool sizes, and incidences of diseases requiring platelet transfusions.

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Introduction

The production of pooled platelet concentrates (PPCs), apheresis platelet concentrates (APCs), red blood cell concentrates (RBCCs), fresh frozen plasma (FFP), and other blood components (e.g. blood coagulation factors) is interlinked. Changes in the production of one blood component may have consequences for the availability and quality of other components.

Data for platelet concentrate (PC) production in France, Germany, Switzerland, and the UK show that so far a significant percentage of produced PCs consists of apheresis platelets (table 1). Clinical guidelines do not differentiate between the application of PPCs or APCs except in patients with immune-mediated transfusion refractoriness and fetal and neonatal alloimmune thrombocytopenia (FNAIT). For those patients, single-donor apheresis platelets matched for human leukocyte antigens (HLA) and/or human platelet antigens (HPA) are recommended [1, 2]. The incidence of FNAIT is one in 1,000 live births [3, 4]. Studies focusing on hemato-oncological patients indicate that platelet refractoriness varies widely (7–34%). The major cause for inadequate platelet increment in this patient collective originates from non-immunologic reasons like fever, infectious diseases, and sepsis with disseminated intravascular coagulation. Moreover, splenomegaly, bone marrow involvement, or cytoreductive chemotherapy also contributes to inferior transfusion success. Immunological causes for platelet refractoriness in hemato-oncology derive mostly from HLA alloimmunization which may be due to prior transfusions as well as prior pregnancy in female patients [5–7].

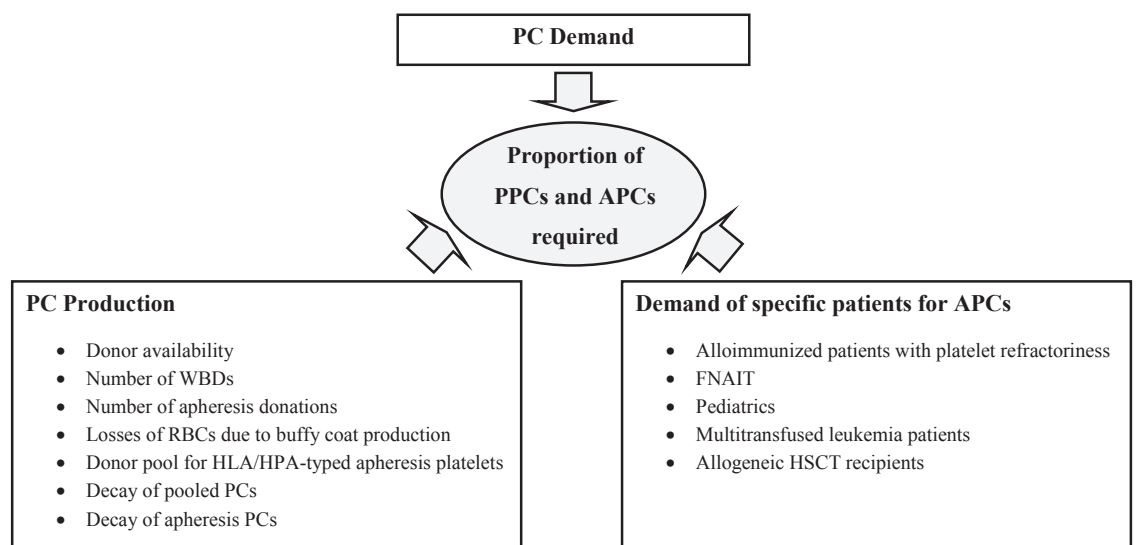
The fact that APCs generally are more costly compared to PPCs accelerates discussions around decreases in the production and supply of APCs. In 2014, the National Health Service Blood and Transplant (NHSBT) has released new recommendations for a reduction of apheresis production of platelets from approximately 80% to 60% of overall platelet provision by the end of 2015/2016 [8, 9]. A clinical model was developed indicating that only about 40%

Table 1. Platelet production in European countries

Country	Proportion of PPC / APC production, number (%)				Changes in total PC production 2012–2013, %	Population-related 2013, PCs / 1,000 population	Reference
	2012		2013				
	pooled PCs	apheresis PCs	pooled PCs	apheresis PCs			
France	154,955 (51.5)	145,728 (48.5)	158,173 (51.6)	148,069 (48.4)	+1.8	4.81	[30–32]
Germany	226,206 (38.4)	362,709 (61.6)	222,228 (38.5)	355,365 (61.5)	–1.9	7.15	[13, 33]
Switzerland	11,650 (34.0)	22,615 (66.0)	12,162 (35.0)	22,588 (65.0)	+1.4	4.34	[34–36]
UK*	40,863 (14.7)	237,212 (85.3)	55,121 (19.3)	230,171 (80.7)	+2.6	4.45	[37–39]

*For the UK, data were from National Health Service Blood and Transplant (NHSBT) only (England and North Wales).

Fig. 1. Model: influences on the proportion of PPCs and APCs required in the future. Reliable models of future PC supply and demand have to consider epidemiological data on PC demand, various aspects of PC production and the special demand of specific patients for single donor APCs. Aspects of future PC production are donor availability, WBDs and apheresis donations, losses of WBDs due to buffy coat production and subsequently



RBCs, the size of the donor pool needed to provide sufficient HLA/HPA-typed platelets for specific patients, and the decay of PCs at the producer. Aspects of the demand of specific patients for APCs are the epidemiology of alloimmunization and FNAIT, the demand in pediatrics, and possible advantages of single-donor APCs for hemato-oncological patients.

single-donor apheresis platelets will be needed to satisfy current patient demands for the following specific patients: i) neonates and pediatrics and ii) patients requiring HLA/HPA matched platelets. The model is financially driven and should help to reduce costs and to implement platelet-additive solution for all PCs. Basis of the model is the assumption that there is no difference in clinical efficacy between apheresis or buffy coat-pooled platelets [8].

In Germany, health insurance companies are increasingly asking for a rationale when single-donor APCs instead of the less costly buffy coat PPCs are provided. This has become evident in a recent decision of the Federal Social Court (March 10, 2015; reference number B 1 KR 2/15 R). In this case, the statutory health insurance did not have to pay for the additional charge for APC transfusion in a cardiac surgery patient [10, 11]. One of the major consequences of a decreasing proportion of APCs used will be that the donor pool for APCs will decline. For Germany in 2010, a total of 36,791 multiple apheresis donors with on average 5 apheresis donations/year were reported [12]. Matching patients with the appropriate HLA/HPA-typed platelets in the future will only be feasible with a sufficiently large pool of apheresis donors.

The focus of this paper is to analyze consequences associated with potential shifts in the supply and use of PPCs and APCs in Germany based on model calculations.

Material and Methods

Model

A model was designed to identify the parameters which influence future PC supply and demand and the proportion of PPCs and APCs required (fig. 1). German epidemiological data on PC demand, various aspects of PC production, and the special demand of specific patients for single-donor apheresis platelets were searched for by literature and desktop researches. Included issues of future PC production were amongst others donor availability, whole blood donations (WBDs) and apheresis donations, losses of WBDs due to buffy coat production, the size of the donor pool needed to provide sufficient HLA/HPA-typed platelets for specific patients, and rates of PC decay.

Model calculations from the societal perspective were conducted based on data from literature and desktop researches. An exemplary 1-year period was selected. The influence of the proportion in PPC and APC production on losses of quality and quantity of erythrocytes during buffy coat separation, on total PC decay at the producer, and on the availability of HLA/HPA typed donors was estimated.

Table 2. Model input: base case*

	Whole blood donations			
	RBCs	total PCs	pooled PCs	apheresis PCs
Production, n (%)	4,371,743 (100)	577,593 (100)	222,228 (38.5)	355,365 (61.5)
Decay at the producer, n (%)	98,945 (2.26)	46,218 (8.00)	26,552 (11.95)	19,666 (5.53)

*Data are from the Paul Ehrlich Institute (PEI) 2013 [13]. Total registered 2013: 4,631,290.

Model Input

PubMed was searched for data on PC supply and demand, on PPC and APC production and transfusion, on platelet refractoriness, on FNAIT, on HLA matching, and on platelet transfusions in hemato-oncological patients. The following searches were conducted: ('Platelet Transfusion/statistics and numerical data'[Mesh] OR 'Platelet Transfusion/therapeutic use'[Mesh] OR 'Platelet Transfusion/therapy'[Mesh] OR 'Platelet Transfusion/utilization'[Mesh]), 'Blood Donors'[Mesh] AND 'Germany'[Mesh], 'Thrombocytopenia, Neonatal Alloimmune'[Mesh], 'Platelet Transfusion'[Mesh] AND 'Immunosuppression'[Mesh], 'Platelet Transfusion'[Mesh] AND 'Leukemia'[Mesh]. In addition, free search terms, e.g. 'pooled platelets' AND 'apheresis platelets' as well as 'hematological malignancies' AND 'platelet transfusion', were applied. Each search was done for the last 10 years. Citations of identified journal articles were searched for further relevant publications. Desktop researches, predominantly internet searches for existing data, were performed. Model input data identified for calculations: Data from the Paul-Ehrlich-Institute (PEI) for the year 2013 on the production of PPCs and APCs in Germany were used [13]. Estimated losses of erythrocytes during production of PPCs were taken from the literature [14].

Assumptions

The following assumptions were made: i) There is no difference reported between PPCs and APCs concerning clinical efficacy [1, 2, 8, 15]. ii) Four WBDs are needed for the production of 4 buffy coats to obtain 1 PPC [15–17]. iii) During buffy coat-derived PPC production from WBDs, a proportion of erythrocytes is lost or damaged. The estimated loss of erythrocytes amounts to 5–10% of the WBDs used [14]. WBDs are used for the production of RBCCs. In Germany, the yield of annual RBCCs from the annual WBDs in 2013 was 94.4% (table 2). Estimated losses in WBDs are converted in estimated final losses of RBCCs. iv) The decay rate at the producer for PPCs and APCs remains approximately stable as in 2013 (table 2) [13] v) APCs will continue to be needed for neonates, pediatric patients, and for patients requiring HLA/HPA matched platelets [2–4, 6, 7].

Base Case

The model calculations for the base case describe the current situation for PPC/APC production in Germany. Base case calculations are based on data from the PEI for the year 2013 (table 2) [13].

Scenarios

Different scenarios were calculated. Proportions of PPCs were assumed to be 10% up to 100% of total PCs produced using the data from the PEI for the year 2013 [13].

Model Output

Model output is expressed as number of WBDs needed for the production of the corresponding amounts of PPCs, as percentage of annual WBDs used for production of PPCs, as the estimated number of WBDs lost annually due to the production of PPCs, as the estimated number of the calculated corresponding RBCCs lost annually, as the estimated percentage of annual RBCCs lost, and as the estimated decay of PCs at the producer in number of PCs and in percent of total PCs produced annually. The expected impact of changes in the proportion of PPCs produced on the pool of HLA/HPA-typed apheresis donors is addressed.

Results

In 2013, a total of 888,912 WBDs were used to produce 222,228 buffy coat-derived PPCs in Germany. This corresponds to 19.2% of annual WBDs. The losses of erythrocytes in these WBDs used for buffy coat PPC production were estimated to amount to 44,446–88,891 WBDs. This corresponds to 41,957–83,913 RBCCs, which is an estimated percentage of annual RBCCs lost in Germany of approximately 1–2%.

Calculations for different scenarios with a proportion of 10% up to 100% PPCs produced were conducted (table 3). Up to a proportion of 20% PPCs, no more than 10% of annual WBDs are used for buffy coat PPC production. The estimated percentage of annual RBCCs lost is 1% or below. The total decay of PCs at the producer is below 40,000 PCs (<7% of total PCs produced). With 60% PPCs produced, the estimated percentage of annual RBCCs lost increases up to 3.0%. This corresponds to an estimated number of more than 130,000 RBCCs lost annually. A total of 54,189 PCs (9.4% of total PCs produced) are lost due to decay at the producer. HLA/HPA-typed apheresis donors are reduced. With a change to 100% PPCs, overall 50% of annual WBDs have to be used for buffy coat production. This leads to an estimated percentage up to 5% of annual RBCCs lost and corresponds to an estimated number of more than 200,000 RBCCs lost annually. The number of PCs lost due to decay at the producer increases up to 69,022 (11.95% of total PCs produced). In addition, the pool of HLA/HPA-typed apheresis donors disappears.

Discussion

Available data for Germany indicate that both types of platelet concentrates, buffy coat-derived PPCs as well as single-donor APCs, are needed to meet the requirements of a flexible and sufficient supply for all kinds of patients [16, 17]. Likewise, in 2011 the German Society for Transfusion Medicine and Immune Hematology already recommended to provide both types of platelets to avoid the hazards of critical shortage in platelet supply [18]. In this context extensive elaborations have been published on different aspects of the PC supply in Germany, e.g., on the quality of APCs compared to PPCs, on reimbursement, on the advantages of decentralized small apheresis donation units close to the hospital, or on the general possibility to shift the total supply to APCs but not to PPCs [11, 15–17, 19–21]. Still the question on the optimal proportion of PPC/APC production for Germany has not been answered.

Table 3. Scenarios for different proportions of PPCs produced*

Percent PPCs of total PCs produced	10	20	30	40	50	60	70	80	90	100
Percent of annual WBDs used for production of PPCs	5	10	15	20	25	30	35	40	45	50
Estimated number of WBDs lost annually	11,552–23,104	23,104–46,207	34,656–69,311	46,207–92,415	57,759–115,519	69,311–138,622	80,863–161,726	92,415–184,830	103,967–207,934	115,519–231,037
Estimated number of RBCs lost annually	10,905–21,810	21,810–43,619	32,715–65,430	43,619–87,240	54,524–109,050	65,430–130,859	76,335–152,669	87,240–174,480	98,145–196,290	114,826–218,099
Estimated percentage of annual RBCs lost, %	0.25–0.5	0.5–1.0	0.75–1.5	1.0–2.0	1.25–2.5	1.5–3.0	1.75–3.5	2.0–4.0	2.25–4.5	2.5–5.0
Decay at the producer: number of PCs	35,649	39,357	43,066	46,774	50,481	54,189	57,898	61,606	65,314	69,022

*In Germany, total WBDs in 2013 were 4,631,290 used for the production of 4,371,743 RBCs (94.4% of WBDs). Total production of PCs was 577,593 units [13]. It is assumed that losses of erythrocytes due to production of buffy coats for PPC production from WBDs amount to 5–10% of the WBDs used [14]. The number of WBDs lost annually, as well as the corresponding number of RBCs otherwise produced from these WBDs can be calculated. As a function of the proportion of PPCs produced the percentage of WBDs used for production of PPCs changes. As a result also the estimated number and percentage of annual RBCs lost due to production of buffy coat derived PPCs are changed. Due to different rates of decay at the producer for PPCs and APCs the overall rate of platelet concentrate decay changes as well (table 2).

Shifting the Supply from APCs to PPCs

Ongoing discussions on increased cost of APCs over PPCs might lead to a potential shift in APC supply towards PPCs. In 2013, the proportion of APCs produced was 61.5% in Germany, 80.7% in the UK, and 48.4% in France (table 1). Mainly driven by financial arguments the NHSBT has recommended in 2014 to reduce APC production stepwise to 60% of the overall platelet provision by the end of 2015/2016. In the UK, it has been estimated that only about 40% of APCs will be needed in the future for specific patients requiring HLA/HPA-matched platelets. However, one might speculate that the target 60% instead of 40% includes an ample safety margin to avoid risks on the side of the apheresis donor pool [8, 9].

To capture the consequences of changes in PPC/APC production in Germany we designed a comprehensive model. The base case describes the current situation of PPC/APC production in Germany with a proportion of 61.5% APCs in 2013 [13]. For the production of 222,228 buffy coat-derived PPCs, a total of 19.2% of the annual WBDs are used. During production of buffy coats for PPCs red blood cells are lost. In total, the calculated losses amount to 1–2% of all RBCs which were donated that year. In scenario calculations we varied the proportion of APC/PPC provision. In case the proportion of APCs is lowered to 40% as has been recommended for the UK, the estimated loss of annual RBCs during the production process of the 60% PPCs will increase up to 3%. This corresponds to an estimated number of more than 130,000 RBCs lost annually, 1.6 times as much as in the base case. Calculations with the assumption of stable decay rates at the producer result in an increase of PC decay from 46,218 PCs (8.0%) for the base case to 54,189 PCs (9.4%) with 60% PPCs.

Development of the Supply with WBDs

In Germany, WBDs decreased from 2011 to 2012 by 3.2% and from 2012 to 2013 by 2.9% [13]. A concomitant reduction in RBC consumption from 2010 to 2011 by 1.3%, from 2011 to 2012 by 2.2%, and from 2012 to 2013 by 6.5% was observed, presumably

due to a more restrictive use of blood products and the introduction of the concept of ‘patient blood management’ [22]. Simultaneously, the number of WBDs per 1,000 inhabitants has decreased from 2011 to 2013 from 61 to 57, whereas the number of apheresis donations per 1,000 inhabitants still increased from 2011 to 2013 from 33 to 34 [13]. This indicates, in accordance with the predicted donor development in Germany in the upcoming years, that the restrictive use in blood products might not be sufficient to balance the decrease in WBDs and the subsequent decrease in the production of RBCs in the future [12]. Expected demographic changes will lead to an aging population with a decreasing number of donors while an increasing number of cancer cases will increase the demand for blood products, especially PCs [23–25]. The shrinking process in the donor population has been predicted to accelerate, in particular after 2015 [23].

Supply with HLA/HPA-Typed Platelets

HLA/HPA-typed apheresis concentrates are indicated for transfusion refractory patients due to HLA antibodies and FNAIT [2, 3, 6, 16, 17]. The shift to PPCs will lead to shrinkage of the HLA/HPA-typed apheresis donor pool. This will be due to a decreased demand of apheresis donations and reduced recruitment of new apheresis donors. Currently, each apheresis center caring for these patients has built up a sufficiently large pool of donors to allow for timely delivery of matched APCs even for rare constellations. However, the number of apheresis donors needed to supply immediate HLA-matched APCs has not been defined. Therefore, it has not been incorporated into the model. It is obvious that substantial problems in achieving the supply of matched APCs can occur.

Major Use of Platelet Transfusions in Hemato-Oncological Patients

Few studies have been published so far on the epidemiology of PC use in terms of distribution of PCs to different patient groups evaluating the need for PPCs or APCs, [26]. One German single-center study showed that 56.6% of all PC transfusions (data for

2011, apheresis only) were given to patients over 50 years of age. Hemato-oncological patients comprised 37.1% of all cases and received 50.9% of transfused units of PCs [27]. A study on PC use in the North of England in 2012 showed similarly that 60.5% of PC transfusions were given to hemato-oncological patients. The median age of PC recipients was 57 years [28]. In our hospital, a total of 10,071 APCs were transfused in 2014 to 1,684 patients, thereof 5,613 APCs to 538 hemato-oncological patients (data on file, Department of Transfusion Medicine, Cell Therapeutics and Hemostaseology, University Hospital of Munich,). A survey of the PEI regarding indications for PC transfusions in 2011 and 2012 showed that approximately 75% of all PCs were transfused in hemato-oncological departments including pediatric divisions [16, 17].

Immunosuppressed hemato-oncological patients require frequent PC transfusions and are prone to infections, allergic reactions, and alloimmunization [6]. Therefore, special subgroups of these patients, e.g. multitransfused leukemia patients or allogeneic hematopoietic stem cell transplantation recipients, might benefit from the use of APCs because of the lower exposure to antigens from a single donor with a possibly lower risk of allergic reactions and alloimmunization. However, prospective comparative studies on the use of APCs and PPCs in subgroups of these patients are currently rare or not available [5, 29].

Limitations of the Model and Future Challenges

The model was designed in a conservative way to avoid overestimations. Model assumptions were based on the scarce data published due to the lack of comprehensive evidence-based data. In consequence the following limitations arise and should be taken into consideration when interpreting the presented results: It was assumed that 4 WBDs are needed to obtain 1 PPC, even though for a certain percentage of the PPCs 5 or 6 buffy coats may be pooled. Due to the lack of representative information on the real number of WBDs used in Germany for the production of PPCs it might be possible, that the amount of red blood cells lost is higher than calculated in the model. Due to a lack of data, it was assumed on the

basis of a published estimation that the loss of erythrocytes amounts to 5–10% of the WBDs used for PPC production. Therefore, the model can only give a range of the corresponding WBDs and RBCCs lost annually. The real number might be even higher. The decay rate at the producer for PPCs and APCs was assumed to remain stable. However, it might as well be the case that decay rates of PPCs decrease and decay rates of APCs increase when the proportion of PPCs to APCs changes to a preponderance of PPCs. Scientific papers have been published in the literature regarding risks of PPCs and APCs for recipients and donors [11, 15–17, 19–21]. The various safety aspects were not considered in the model. A comprehensive model should include data on efficacy and effectiveness of PPCs and APCs. However, so far no prospective randomized studies on clinical efficacy or comparative observational studies on the effectiveness of buffy coat PPCs and single-donor APCs have been published.

Conclusion

In conclusion, model calculations were provided to increase transparency on the sensitiveness in the context of blood production and blood supply. The impact of shifts in the production of PPCs and APCs on blood product supply in Germany was chosen as an example. To predict the optimal proportion of pooled PCs and single-donor apheresis PCs, reliable data are needed on PPC production, loss of erythrocytes, future PC demand, donor availability and future donations, donor pool required for HLA/HPA typed apheresis platelets, decay of pooled PCs and apheresis PCs, and demand of single-donor apheresis PCs for specific patients.

Disclosure Statement

The authors state that they have no conflicts of interest to disclose.

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