Nationwide Implementation of Pathogen Inactivation for All Platelet Concentrates in Switzerland

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Keywords

Blood safety · Platelet concentrates ·
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Summary

Introduction: Bacterial contamination of platelet concentrates (PCs) has been identified as the most prevalent transfusion-associated infectious risk. To prevent PC-related septic transfusion reactions, the Intercept[®] pathogen inactivation procedure was introduced for all PCs in Switzerland in 2011. **Methods:** Based on numbers of transfused units and mandatorily reported adverse events with high imputability, we compare the risks associated with transfusion of conventional PCs (cPCs) and pathogen-inactivated PCs (PI-PCs). **Results:** From 2005 to 2011, a total of 158,502 cPCs have been issued in Switzerland, and 16 transfusion-transmitted bacterial infections (including 3 fatalities) were reported. This corresponds to a morbidity and mortality rate of ca. 1:9,900 and 1:52,800, respectively. From 2011 to 2016, a total of 205,574 PI-PCs have been issued, and no transfusion-transmitted bacterial infection was reported. Despite continuously increasing transfusion reaction rates per 1,000 RBC and plasma issued between 2008 and 2016, we observed reductions of 66% for life-threatening and fatal reactions and of 26% for all high-imputability transfusion reactions related to PI-PCs as compared to cPCs. No increased rates of bleeding or clinical observations of ineffectiveness of PI-PCs have been reported. After im-

plementation of PI-PCs, the annual increase in platelet usage per 1,000 inhabitants decelerated. **Discussion:** Swiss hemovigilance data confirm a favorable safety profile of the nationwide introduced Intercept pathogen inactivation procedure and its reliable prevention of septic transfusion reactions and fatalities due to bacterially contaminated PCs.

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Introduction

Bacterial contamination of blood components has been identified as the most prevalent transfusion-associated infectious risk. Because platelet concentrates (PCs) are stored at $22 \pm 2^\circ\text{C}$, they provide a favorable environment for bacterial growth; therefore, septic transfusion reactions are most often due to transfusion of contaminated PCs [1–3].

The blood supply for Switzerland's population of 8.4 million inhabitants is maintained by the Blood Transfusion Service of the Swiss Red Cross as umbrella organization with its 11 (until 2014 13) regional services. Transfusions are administered in about 200 hospitals. Four centers (including one pediatric center) perform allogeneic hematopoietic stem cell transplantations. Reporting of suspected transfusion reactions is mandatory since 2002. The Swiss Hemovigilance data originating from this spontaneous reporting system are analyzed by Swissmedic, the Swiss Agency for Therapeutic Products. Between 2005 and 2009, approximately 1.6 mil-

lion red blood cell concentrates (RBCs), 350,000 units of plasma, and 120,000 PC's were issued for transfusion. In the same period, 16 febrile/septic reactions (including 3 fatal reactions), documented to be due to bacterially contaminated PCs, were reported.

Based on these figures, we estimated that at that time in Switzerland roughly 1 out of 8,000 PC transfusions would result in an adverse reaction due to bacterial contamination of the component. A life-threatening transfusion reaction was to be expected in 1:14,000 PC transfusions and death of the recipient in around 1:40,000 PC transfusions. Hence, statistically speaking, roughly every 1.6 years a patient would die because of bacterial contamination of a PC [4]. In general, transfusion risks may be underestimated as a result of under-reporting in passive reporting systems like the Swiss Hemovigilance system, and for this reason the risks described here should be understood as minimum figures.

In the second half of 2009, the Intercept® technology for pathogen inactivation of PCs was approved for use in Switzerland [5].

The procedure is based on the addition of the psoralen compound amotosalen HCl to the PC suspended in 65% intersol or SSP+ additive solution / 35% plasma, resulting in an amotosalen concentration of 150 µmol/l. The amotosalen intercalates between the pyrimidine base pairs of nucleic acids. Upon UVA illumination with an energy of 3 J/cm² at 320–400 nm wavelength, it forms covalent bonds, preventing further replication and thus inactivating pathogens as well as residual leukocytes. A compound absorption device reduces the amotosalen residual content to <2 µmol/l in the PC product for transfusion, which can be stored for up to 7 days [6].

Having regulatory oversight pertaining to the safety of medicines and taking notice of this situation, Swissmedic informed the Blood Transfusion Service of the Swiss Red Cross that it was clearly indicated to take suitable measures to reliably prevent clinically relevant bacterial contamination of PCs and to introduce them as soon as possible.

Expected Impact of Nationwide Pathogen Inactivation for all PCs

We expected the universal use of pathogen-inactivated PCs (PI-PCs) to result in complete cessation of septic transfusion reactions due to PCs as well as in a general decrease in number and severity of transfusion reactions [7, 8]. Based on former experiences with production of PI-PCs for clinical trials in the university hospital of Basel, we assumed that an increase in PC collection of approximately 15% would be necessary to provide the amount of PCs that would be requested for transfusion. The ongoing scientific dispute about the clinical effectiveness of PI-PCs indicated a potentially limited acceptance of the new components by the clinicians. Lower corrected count increments for PI-PCs compared to conventional PCs (cPCs) with unclear clinical significance were reported by meta-analyses [9, 10]. Additionally, acute respiratory distress syndrome (ARDS) was described in significantly more patients having received PI-PCs (5/328) than in those transfused with cPCs (0/327) [11]. A similar trend was seen following re-analysis of the data by independent experts (although not statistically significant anymore) [12]. Taking into consideration experimental data showing

lung injury in lipopolysaccharide-treated mice following transfusion of UVB-irradiated PCs, whereas no lung-injury was observed following transfusion of non UV-irradiated PCs to otherwise identically treated mice [13], we still considered TRALI (transfusion-associated lung injury) in association with PI-PCs a potential risk.

Material and Methods

In order to decide about the measure(s) to be taken to address the risk related to bacterial contamination of PCs on a rational basis, we evaluated various options, i.e., reduction of the maximal storage time from 5 to 4 days, universal bacterial screening of PCs, and pathogen inactivation. For this evaluation, we analyzed scientific publications, published hemovigilance data, unpublished Swiss Hemovigilance data, and proprietary information included in the dossier submitted to Swissmedic for marketing approval of the Intercept procedure.

After having taken the decision to implement pathogen inactivation for all PCs in Switzerland, we planned the implementation, its evaluation, and the assessment of the important potential risk of TRALI in association with PI-PCs.

The implementation and its effect on the safety profile of PCs was evaluated based on analysis and comparison of Swiss Hemovigilance case reports with high imputability (causal relationship with the transfusion 'probable' or 'certain').

To assess the potential risk of TRALI in association with PI-PCs, we re-analyzed the raw data of all 160 high-imputability transfusion reactions pertaining to PI-PCs reported in 2011 and 2012 and prospectively applied an active search strategy for respiratory symptoms in all reports related to platelet transfusions from 2013 onwards.

Results

Swissmedic and the Blood Transfusion Service of the Swiss Red Cross jointly decided to introduce the Intercept pathogen inactivation procedure for all PCs in Switzerland.

Shortly after we had communicated this decision to the transfusion medicine community in Switzerland, information about a HOVON trial (Hemato Oncology Foundation for Adults in the Netherlands) was presented at the AABB annual meeting 2009 [14]. The investigators informed that the data safety monitoring board had advised them to stop enrolling patients due to a statistically significant elevation of bleeding events in patients following transfusion of amotosalen/UVA-treated PI-PCs compared to patients having received transfusions with cPCs.

To estimate the impact of this finding on the safety profile of PI-PCs and to address the concerns the presentation raised among the transfusion medicine community in Switzerland, we evaluated the limited data on the HOVON trial available to us at that time [14]. Despite our request to the authors, no data other than that presented in the abstract book was provided. Hence we decided to continue with the nationwide implementation project and, should more qualified information become available indicating serious safety concerns, reconsider our decision.

Stages and Challenges of the Implementation

The implementation plan defined an incremental approach including all (at that time) 13 regional blood transfusion services and

intended all PCs for routine use to be treated with the Intercept procedure by the end of 2011. Between July and October 2010, three pilot centers (Basel, Lausanne, and Zürich) planned and performed the validation of adapted production methods and of the pathogen inactivation procedure for PCs.

Adaptations of the manufacturing process included but were not limited to:

- introduction of the use of platelet-additive solutions (SSP+ or intersol)
- delayed product release due to UVA illumination and absorption of residual amotosalen
- additional work load and cost for material
- the implementation of the buffy coat method for pooled PCs in centers that had exclusively produced apheresis-derived P's so far
- assuring that all products comply with the Intercept guardbands (255–325 / 300–420 ml; $2.5\text{--}6.0 \times 10^{11}$ / $2.5\text{--}7.0 \times 10^{11}$ platelets, ratio plasma / additive solution)
- intensified search for and selection of donors suitable for double-dose apheresis donations (platelet count $>230\text{--}250 \times 10^9/\text{l}$)
- adaptation of apheresis collections to twin products (double dose, e.g. 5.4×10^{11} for apheresis procedures)
- keeping volume loss < 50 ml/inactivation set.

The results demonstrated that the guardband criteria specified by the manufacturer and necessary to provide products suitable for the pathogen inactivation procedure were predictably met and that the latter was reliably performed, leading to final products within the defined specifications.

Following data review and center-specific authorization by Swissmedic, these centers launched production of PI-PCs for clinical use in January 2011. The other regional blood transfusion services performed validations based on the same protocols and started routine production in the course of 2011.

Since then, 'The new Swiss Platelet Unit' has the following specifications:

- $\geq 2.4 \times 10^{11}/\text{unit}$
- pathogen-reduced (80% of all PCs produced in 2011 → 100% since November 2011)
- platelet-additive solution ($\sim 30\%$ in 2010 → 100% in November 2011)
- 7-day storage (voluntarily restricted to 5 days until July 2013)
- apheresis or pooled buffy coat-derived PCs (currently $\sim 35\%$ pool buffy coat-derived PCs)
- residual amotosalen concentration $< 2 \mu\text{mol/l}$.
- residual erythrocyte and leukocyte count $< 4 \times 10^6/\text{ml}$ and $< 1 \times 10^6/\text{unit}$, respectively.

The routine quality control parameters of PI-PCs in Switzerland include visual control for bag defects, turbidity, color alterations, hemolysis, clots, and swirling of all units issued. In 1% of units issued each month, verification of the minimal volume of 150 ml is recorded. For 10 components each month, confirmation of the minimal platelet content ($>2.4 \times 10^{11}/\text{unit}$) before and after inactivation, residual erythrocyte and leukocyte counts of

Table 1. Septic transfusion reactions (fatalities) per year before and after pathogen inactivation implementation^a

Year	Conventional platelet component transfusion-related sepsis (fatal) ^b	INTERCEPT platelet component transfusion-related sepsis (fatal) ^c
2005	6 (2)	
2006	2 (0)	
2007	2 (0)	
2008	2 (0)	
2009	3 (1)	
2010	1 (0)	
2011	0 (0)	0 (0)
2012		0 (0)
2013		0 (0)
2014		0 (0)
2015		0 (0)
2016		0 (0)
Total	16 (3)	0 (0)

^aTwo-sided Fisher's exact test $p < 0.001$.
^bTotal units 158,502.
^cTotal units 205,574.

$< 4 \times 10^6/\text{ml}$ and $< 1 \times 10^6/\text{unit}$, respectively, and the (minimal) pH of >6.4 at 22°C at the end of the maximal storage time are confirmed.

Between April 2013 and March 2014, the Swissmedic Official Medicines Control Laboratory conducted a market surveillance activity. During this period, amotosalen residual content was measured in 570 PI-PCs provided by all 13 regional blood transfusion services ($\approx 1.6\%$ of all PI-PCs issued in this period). Based on the observed robust performance of the depletion process and the established safety margin for amotosalen [15], the national regulatory agency decided not to perform further measurements of the amotosalen residual content, unless relevant changes to the procedure are introduced or any other indication is noticed.

Observations Following Introduction of PI-PCs

With respect to daily practice in the blood transfusion centers, the implementation was described as quite smooth, the proportion of pooled, buffy coat-derived PCs has increased, and better standardization of platelet components was observed. Until July 2013, shelf life of PI-PCs was restricted to 5 days on a voluntary basis. Since then, storage for up to 7 days is practiced resulting in fewer products having to be discarded due to reaching their expiry date.

Between 2005 and 2011 a total of 158,502 conventional PCs have been issued in Switzerland; during this period, 16 transfusion-transmitted bacterial infections (including 3 fatalities) had been observed. From 2011 onward, 205,574 PI-PCs have been issued until end of 2016, and no transfusion-transmitted bacterial infection following transfusion of PCs was reported [16, 17] (table 1). Moreover, earlier results indicating fewer transfusion reactions in general following PI-PCs compared to cPCs have also been confirmed. When comparing the rates (transfusion reactions reported

Table 2. Transfusion reactions related to cPCs and PI-PCs

Transfusion reactions	2008–2011 cPCs (93,600 units transfused)		2011–2016 PI-PCs (205,574 units transfused)		Risk reduction PI-PCs vs. cPCs
	reports	risk	reports	risk	
High imputability total	344	~1:270	555	~1:370	–26%
High imputability severity grade 3 and 4	33	~1:2,800	25	~1:8,200	–66%

per 1,000 components issued for transfusion) related to cPCs (2008–2011) and PI-PCs (2011–2016) in Switzerland, a decline of 66% for life-threatening and fatal reactions and of 26% for all high-imputability transfusion reactions is observed (table 2). The total reduction of transfusion reactions correlates with fewer allergic transfusion reactions, most likely due to the overall lower plasma content of PI-PCs compared with c-PCs in Switzerland.

Similar figures were observed for France. According to hemovigilance reports, a total of 2,130,970 cPCs were issued for transfusion in France between 2005 and 2015. 57 transfusion-transmitted bacterial infections (including 11 fatalities) were reported in association with cPCs. The number of PI-PCs issued in the relevant period amounts to more than 300,000, with no transfusion-transmitted bacterial infection reported [18, 19].

During the observation periods, 73 transfusion-transmitted bacterial infections (including 14 fatalities) related to cPCs were reported in the two countries in total, whereas none were observed in association with PI-PCs.

Following implementation of pathogen inactivation for all PCs in Switzerland, the annual increase in platelet usage per 1,000 inhabitants has decelerated compared to the previous years [16]. In comparison to other European countries, we do not transfuse more platelets even though there is no other country that exclusively uses PI-PCs which are suspected to potentially be less effective [20].

In a retrospective analysis of all reported cases of TRALI with regard to which kind of PCs had been transfused to the patient – either alone or in combination with other blood components – we could not substantiate the hypothesis that PI-PCs might be associated with an increased risk for TRALI compared to cPCs [16, 17].

Discussion

Reduction of Storage Time from 5 to 4 Days

Retrospective analysis of all reports with imputability ‘probable’ or ‘certain’ (= ‘high imputability’) received between 2005 and 2010 in Switzerland reveals that a reduction of storage time to a maximum of 4 days would indeed have prevented 5 transfusion-transmitted bacterial infections, thereof 2 fatalities and 1 life-threatening transfusion-associated sepsis. However, 9 transfusion-transmitted bacterial infections, including 1 fatality and 5 septic reactions, representing the majority of reported cases, would still have occurred. For two cases dating from 2005 or 2006, documentation was insufficient to decide whether a maximum storage duration of 4 days would have prevented them. Even if these 2 cases had been prevented by 4-day storage, the effectiveness of this measure would

only add up to 50% or less. These data are in line with results from SHOT (Serious Hazards Of Transfusion; hemovigilance scheme of the UK) data from the years 1995 to 2009 describing 38 cases of platelet-related transfusion-transmitted bacterial infections with 21 pertaining to components stored for 1–4 days, 12 stored for 5 days, and 6 with storage duration not sufficiently documented (personal communication; Stephan Thomas, NHSBT Brentwood, UK) [21].

Bacterial Screening

Several methods with different performances are available to detect presence or growth of bacteria in PCs (swirling, pH or glucose measurement, Gram or acridine orange staining, nucleic acid amplification and detection (rRNA and PCR), and cultural methods (e.g. automated blood culture systems)). In summary, one can conclude that the detection limit of a method inversely correlates with the time it needs to produce a final result. This indicates that when introducing bacterial detection methods to enhance bacterial safety of PCs, we may encounter problems with sensitivity, specificity, or delayed availability of test results [21–26]. Unfortunately, the concerns raised pertaining to sensitivity, specificity, and time delay are not only theoretical ones, they also emerge in daily clinical practice as published data from different countries confirm.

A widely used culture-based method is bacterial screening by the automated BacT/ALERT 3D® system (bioMérieux Suisse S.A., Geneva, Switzerland) using a sample taken from the component within the first 24 h of storage. In the Netherlands, bacterial screening is carried out on 100% of PCs by the BacT/ALERT 3D system. The claim that this screening proves to be successful in preventing the seriously contaminated PCs from entering the transfusion chain [12] is contested by reports from the USA, Canada, and Germany where the same screening system has been used. These countries describe cases of death resulting from bacterially contaminated PCs in up to 1:52,000 PC transfusions and conclude that bacterial screening may fail to identify over 50% of contaminated products, thus incurring the risk of septic transfusion reactions as a consequence of false-negative results in up to 1:26,000 transfusions [27–31].

Based on these observations, we concluded that neither by reducing the maximum storage time to 4 days nor by introducing bacterial screening, we would be likely to reach our goal of reliably preventing clinically relevant bacterial contamination of PCs in Switzerland.

Pro and Contra Pathogen Inactivation

Following approval of the Intercept procedure in 2009, a method for pathogen inactivation of PCs was available in Switzerland.

Table 3. Pros and cons of introducing the amotosalen-UVA method for pathogen inactivation

Advantages	Disadvantages
Procedure is effective for the majority of bacteria, viruses and protozoa including emerging pathogens and non-tested agents	missing data on long term safety
(Expected) decrease in transfusion reactions	loss of ca. 10–15% of platelets and modestly of in vitro function costs (0.2–1.4 Mio USD/QALY [32–34] (but compare: 2.7 Mio USD/QALY for additional Hep B/C and HIV NAT)
γ -Irradiation superfluous	single provider of method approved in Switzerland
Stop CMV screening! & others?	
Relax donor exclusions? (travel, ...)	
Expected reduced expiration rate: <3%	
Increased rate of pooled platelet concentrates	
Gain of additional plasma (use of PAS)	

Based on data submitted for marketing authorization, the procedure was effective against the majority of bacteria, viruses, and protozoa, including emerging pathogens and such for which no tests are performed (yet). Additionally, γ -irradiation to prevent transfusion-associated graft-versus-host disease would no longer be necessary for components treated with amotosalen and UVA. Discontinuation of screening for CMV and other infections for selected recipient populations seems feasible and relaxation of certain donor deferral criteria could be considered.

On the other hand, reliable data on potential risks due to rare adverse events and on long-term safety of PCs treated with amotosalen and UVA were not available. Furthermore, in vitro as well as clinical trial data indicated a loss of approximately 10–15% of platelet content in the final product and modestly of in vitro platelet function. Considerable costs of 0.2–1.4 Mio USD/QALY were a major concern aiming at a reliable and also affordable blood component supply. Compared to costs of 2.7 Mio USD/QALY for additional HB/-HC/-HIV-NAT which had already been introduced in Switzerland, the costs for pathogen inactivation seemed within the proportion perceived as acceptable by society for measures to improve transfusion safety [32–34]. One further concern from the point of view of reliability of supply was the fact that only one system from a single provider was available.

Based on the above considerations and taking into account the pros and cons as listed in table 3, we concluded that pathogen inactivation would lead to the highest increase in transfusion safety in Switzerland at that time and that its benefits would clearly outweigh the potential risks.

Hemovigilance data available today show that with the implementation of pathogen inactivation for all PCs in Switzerland we have achieved the aim of reliably preventing septic transfusion reactions and fatalities due to bacterially contaminated PCs. They were previously associated with a morbidity and mortality of 1:9,900 and 1:52,800 PCs issued for transfusion, respectively. Including preliminary hemovigilance data of 2017, this correspondingly indicates that we may have prevented up to 20 transfusion-transmitted infections including 4 fatalities during the past 7 years. Additionally, a substantial reduction of overall and life-threatening transfusion reaction reports related to PCs has been observed in the Swiss spontaneous reporting system despite increasing reporting rates in general and for the other blood components (RBCs and

plasma) in particular. The increase of PC requirements in daily clinical practice has turned out markedly less steep than expected based on data originating from clinical trials and does not exceed the increases observed in other European countries where the majority of PC transfusions are covered by cPCs. No reports of increased bleeding or clinical observations of ineffectiveness of PI-PCs have been received to date. Nationwide implementation of the pathogen inactivation procedure for all PCs was completed within 12 months, and a quite smooth implementation of pathogen inactivation in all Swiss blood transfusion services was reported. The proportion of buffy coat-derived PCs increased from 14 to 35%, offering additional sources for the production of PCs, particularly to centers that had been reluctant to distribute buffy coat-derived products due to concerns about their bacterial/viral safety. Product standardization has increased with respect to platelet content, additive solution, and total volume. Last but not least, a decrease of PCs outdated and therefore destroyed to currently ~3% has been observed following introduction of the maximal storage duration of 7 days and further savings could be realized by abrogation of PC γ -irradiation.

Taken together the outlined results of the implementation of PI-PCs completely satisfied our expectations. On December 19, 2014, the US Food and Drug Administration announced on its website the approval of the Intercept Blood System for platelets, mentioning hemovigilance data from France and Switzerland that supported the use of PCs treated by the Intercept system [35].

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Disclosure Statement

The authors declare that they have no conflicts of interest relevant to the manuscript submitted.

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