PROGRAM OF ABSTRACTS

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Quantifying Residual Red Blood Cells In Platelet and Plasma Components: Flow Cytometry and a Visual Inspection Tool Support Implementation of Pathogen Inactivation

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BACKGROUND: Platelet concentrates (PC) and plasma components may contain small numbers of residual RBCs (rRBCs), an important consideration for use of pathogen inactivation (PI) technologies. The INTERCEPT PI blood system (Cerus Corporation) requires that input PC and plasma components have rRBC counts < 4 x 10^6/mL. However, enumeration of rRBC counts can be challenging and there is no consensus method. To support Canadian Blood Services' implementation of the INTERCEPT blood system to produce apheresis and pooled (whole blood (WB)-derived) platelets, psoralen treated, we developed a flow cytometry assay to count rRBCs and an in-house visual inspection tool (VIT) to assess suitability of platelet components for INTERCEPT treatment.

AIMS: To describe a flow cytometry assay and a method for development of a visual inspection tool to assess rRBCs levels in non-RBC blood components prior to pathogen inactivation using INTERCEPT.

METHODS: To count rRBCs, we developed a flow cytometry protocol based on the BD Leucocount Kit. The approach used BD Trucount™ Tubes, which contain a known number of fluorescent beads, as an internal reference to determine absolute cell counts. PCs (apheresis or pooled in 40% plasma/60% SSP+) or plasma (apheresis or WB-derived) were diluted 10X in PBS and added (20 μL) to Trucount™ tubes. RBCs were labelled with CD235a (Glycophorin A)-PE for 30 minutes in the dark at room temperature. Samples were diluted with 1 mL PBS, vortexed and acquired (stopping collection: 2,500 beads) on a BD FACS Canto II running FACSDiva Software version 8.0.1. A gating strategy based on glycophorin-A positive events was applied consistently across samples to ensure only RBCs were counted. To develop a visual inspection tool, platelet components were spiked with known RBC concentrations from an ABO-matched red cell concentrate (1 x 10^6 rRBC/mL; 4 x 10^6 rRBC/mL; and 6 x 10^6 rRBC/mL), photographed and colour-true prints were generated. The visual inspection tool was validated using PCs spiked with known rRBC counts. These PCss were visually assessed next to the VIT by a minimum of 10 users to determine pass or fail against the 4 x 10^6 rRBC/mL limit.

RESULTS: Serial dilutions of plasma or PCs demonstrated linearity of the flow cytometry assay up to 1,500 RBC events. At counts greater than 1,500, the assay undercounted rRBC. Within- and across-run measurements of assay precision resulted in intra-assay coefficients of variation (CVs) ranging from 2.55 to 3.36% (n = 5 samples; 9 runs on each) and inter-assay CVs ranging from 2.02 to 5.12%. (n = 5 replicate samples counted in independent runs). Spiking apheresis PCs with known concentrations of RBCs between 0 and 6 x 10^6 rRBC/mL demonstrated the assay's accuracy (correlation coefficient 0.9997). PCs spiked with known RBC counts were prepared and photographed to develop the visual inspection tool. Validation of the tool by multiple users confirmed its utility to distinguish whether spiked units passed or failed against the 4 x 10^6 rRBC/mL limit.

SUMMARY/CONCLUSIONS: The flow cytometry assay was found to be suitable for counting low numbers of rRBCs in platelet and plasma components. The visual inspection tool was successfully deployed and is being used operationally at Canadian Blood Services to determine the suitability of platelet components intended for INTERCEPT treatment.

The Impact of Pathogen Reduction Technology for Platelets on the Incidence of Transfusion Reactions – A Single Center Study

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INTRODUCTION: The incidence of platelet-related non-hemolytic transfusion reactions (TRs) is considered 10%-30% per transfusion (allergic 1%-2%), ranging from mild to severe, the incidence of septic transfusion reactions (STRs) is lower (approx. 1:10.000 per transfusion), but often severe to lethal. Prevention of STRs and a significant reduction of (allergic) TRs (between 26% and 66% of general TRs in Switzerland and 52% of platelet-related TRs in Strasbourg) was reported as consequence of treating the platelets with pathogen reduction technology (PRT). The reduction of TRs by PRT was mainly due to efficient inactivation of contaminating white blood cells in the platelet unit (while the additional implementation of PAS contributed to the reduction of TRs as well, mainly due to antibody and plasma factors depletion). We implemented PRT for platelets in 2022 to improve the clinical outcome and well-being of patients.

OBJECTIVE: Assessment of the impact of the introduction of PRT for platelets on the incidence of transfusion reactions.

MATERIAL & METHODS: Platelets in 100% plasma were collected at the King Fahd Medical City (KFMC) Blood Center (Riyadh, KSA) either by apheresis (Trima, Terumo-BCT, U.S.A., and MCS+, Haemonetics, U.S.A.) or from whole blood donations (processed with an automated Reveos device, Terumo-BCT). 5 Reveos IPUs were pooled for one adult transfusion dose ($\geq 3x10^{11}$ platelets/unit). Apheresis platelets were treated with amotosalen/UVA PRT (INTERCEPT Blood System, Cerus Corp, U.S.A) from 02/2022, whole-blood derived platelets from 09/2022. In 2023, approx. 50% of platelets issued were pathogen-reduced. The incidence of transfusion reactions was collected by an in-house passive reporting system. Data was analyzed in 3 periods, P1 (2021, conventional platelets); P2 (2022, transition to 50% PR platelets), P3 (2023, 50% PR platelets).

RESULTS: In P1 33.907 (27.2% platelets), in P2 33.921 (23.6% platelets) and in P3 37193 (22.1% platelets) blood components were transfused at the KFMC in total. The number of RBCs transfused per platelet transfusion was in P1 1.93, in P2 2.25, an in P3 2.33. The incidence of general transfusion reactions (all components per 1000 transfusions) was steadily declining during the study period (P1 1.18, P2 1.03, P3 0.81). The rate of platelet-related transfusion reactions per 1000 platelet transfusions (absolute numbers between 11 and 15 per year) was 1.19 in P1, 1.87 in P2 and 1.46 in P3. The rate of total allergic transfusion reactions (absolute number between 13 and 30) per 1000 transfusions decreased between P2 and P3 of 47% (0.71 in P1, 0.6 in P2 and 0.32 in P3). The rate of non-hemolytic transfusion reactions did not change significantly (0.38 in P1, 0.44 in P2, 0.32 in P3), the incidence of other transfusion reactions was too low for a meaningful analysis.

CONCLUSIONS: Our preliminary data points towards a reduction of allergic transfusion reactions (47%) after partial implementation of PRT for platelets as described previously. The number of RBC transfusions per platelet transfusion, as a surrogate marker for bleeding, was not increased.

Cold-Storage of Amotosalen-UVA Pathogen-Reduced Buffy-Coat Platelet Concentrates for Up to 21 Days: Biochemical and Functional Characterization, and Identification of Platelet Subpopulations

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BACKGROUND: Current platelet transfusion requirements are evolving rapidly, with a significant increase in the need for therapeutic platelet transfusions compared to prophylactic transfusions. In this context, cold-stored platelets have gained interest owing to their specific potentially advantageous characteristics, which however require thorough *in vitro* characterization during storage.

AIMS: To assess the effects of cold storage on the *in vitro* quality of buffy-coat (BC) platelet concentrates (PCs) treated with amotosalen-UVA pathogen reduction and stored in PAS-E (SSP+) additive solution for up to 21 days.

METHODS: A pool-and-split strategy was used to obtain double-dose BC-PCs collected into PAS-E/plasma (55%/45%) treated with amotosalen-UVA and stored i) at 22-24°C with constant agitation or ii) at 4°C without agitation.

RESULTS: Platelet counts declined similarly in both groups of PCs during storage without appearance of macroscopic aggregates, while platelet swirling was lost in PCs stored at 4°C, with platelets having a spherical shape as visualized by scanning electron microscopy. Storage at 4°C resulted in a significant reduction in glucose consumption and lactate generation as compared to storage at 22°C as of day 7, and a progressive decrease in pH, which however remained above 6.5 at day 21. Notably, sufficient glucose was still available on day 14 in PCs stored at 4°C, unlike in PCs stored at 22°C. Multicolor flow cytometry analysis for markers of platelet activation, apoptosis and mitochondrial membrane potential revealed emergence of several platelet subpopulations during storage. Among these, the resting, activated, aggregatory, procoagulant, apoptotic and senescent platelets are of prime interest for a better understanding of the functional properties of platelets. Spontaneous exposure of P-selectin, a marker of α-granule secretion, and of phosphatidylserine, a marker for platelet activation and apoptosis evaluated by annexin V binding, were significantly increased in PCs stored at 4°C as compared to 22°C during storage. Mitochondrial transmembrane potential, evaluated using the tetramethylrhodamine methyl ester fluorescent dye retained in functional intact mitochondria, decreased more rapidly in PCs stored at 4°C as compared to 22°C. The subpopulation of resting platelets remained predominant on day 7 at 22°C, while at 4°C this subpopulation was replaced by an equal proportion of procoagulant and apoptotic platelets, the latter becoming dominant on day 21 (**Table**). Finally, the ability of platelets to form thrombi on collagen in a microfluidic chamber was conserved until day 14 at 4°C but only until day 7 at 22°C.

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CONCLUSION: Amotosalen-UVA pathogen-reduced BC-PCs stored at 4°C displayed preserved metabolism, increased spontaneous activation and apoptosis, and preserved *in vitro* platelet adhesive properties for at least 14 days. Further experiments are aimed at better understanding the characteristics and functions of the various emerging platelet subpopulations, which may lead to the development of new or improved platelet products to enhance inventories and access to platelet hemostatic support for bleeding patients.

	Day 1		Day 7		Day 14		Day 21	
Temperature (°C)	**22**	**4**	**22**	**4**	**22**	**4**	**22**	**4**
Resting %	84±1	-	64±1	13±5	27±1	3±1	3±1	5±5
Activated %	9±0	-	29±2	31±14	18±5	8±7	3±2	8±9
Aggregatory %	0	-	0	2±2	2±1	2±0	2±1	1±0
Procoagulant %	0	-	1±0	16±6	4±1	23±2	1±0	9±2
Apoptotic %	5±2	-	3±1	20±17	33±2	36±1	50±5	48±19
Senescent %	0	-	2±0	2±1	5±3	8±3	12±1	18±4
Undefined %	1±0	-	2±0	15±3	11±3	21±1	29±5	12±3

Development of a Preparation Method for Double Dose Platelet Concentrates Obtained from Individual Platelet Units and Ready for Amotosalen/UVA Treatment

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BACKGROUND: Pathogen reduction (PR) of platelet concentrates allows reducing the risk of transmission of infectious agents due to pooling. This benefit has triggered the development of platelet concentrate (PC) preparation methods with up to 8 buffy coats using amotosalen/UVA (A-UVA) PR treatment (INTERCEPT™ Blood System). Alternately, an automated whole blood separation technique (Reveos®) delivers Intermediate Platelet Units (IPU) ready for pooling. Increasing the pool size to 7-8 IPU instead of the usual 4-5-IPU can also be considered for the preparation of PR treated double dose PC.

AIMS: The objective of the study was to determine the feasibility of pooling 7 or 8 IPU to prepare double dose PC, meeting after PR treatment with A-UVA the specifications outlined in the European (EDQM) and Spanish (CAT) guidelines.

METHODS: IPU are obtained from 450 mL ±10% donations on the day of collection and rested for 1 hour before overnight storage under controlled agitation. The target volume is calculated to be 28 mL for 7 BC and 25 mL for 8 BC pools to obtain after addition of 250 mL PAS (T-PAS+) a volume lower than 420 mL and a plasma ratio below 47%. Pools of either 7 or 8 IPU are constituted and filtered for leukocyte depletion without delay in a Reveos platelet pooling set. Platelet counts, volumes and plasma ratio are measured to compare with the A-UVA process entry and final PC specifications. In this development phase, IPU not selected for their platelet content are used to determine platelet recovery and extrapolate what would be the minimum Platelet Yield Index (PYI, selected on the Reveos TOME IPU triage tool) to use for meeting the EDQM and CAT specifications particularly for platelet content, respectively $\geq 2.0 \times 10^{11}$ and $\geq 2.4 \times 10^{11}$ in 90% of the PC. The 28 ml IPU's not used for pooling of 7 were used to make simple pools of 5 units.

RESULTS: **Table 1** shows key performance indicators of the A-UVA PC preparation process without PYI selection of the IPU. These preliminary results indicate that the EDQM requirement for platelet content could be met in at least 90% of the units (100%) but only in 57% of the units using the CAT requirements with both 7 and 8 IPU processes, not selecting the IPU. The simulation indicates that selecting IPU with a minimum average PYI in the pool of ≥60 would allow producing enough double dose PC meeting the requirements from both guidelines and the supply needs. **Table 1** also shows that 100 % pools of 7 IPU, 28 ml, PYI > 60, selected met EDMQ requirements and 80% met CAT requirements.

All pools in this study met the requirement of $< 1 \times 10^6$ residual leukocytes.

SUMMARY/CONCLUSIONS: Both methods of pooling 7 or 8 IPU to obtain platelets compatible with the A-UVA (INTERCEPT) process entry requirements are doable. A selection of IPU with a PYI ≥60 would allow meeting the platelet content specifications in the EDQM and CAT guidelines. Pooling 7 BC is the preferred method if confirmed to be suitable in routine because using IPU of a standard volume of 28 mL.

In addition, the leukoreduction filter used for the pools is valid for up to 8 units.

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Table 1: Key Performance Indicators of the A-UVA PC Preparation Process Without PYI Selection of the IPU

	IPU Pool				PLT			IBS PLT			Standards	
Pool 8 IPU	IPU Volume (mL)	IPU PYI	Potential Yield ($x10^{11}$)	PLS Ratio(%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	EDQM	CAT
N = 14	=25		>6.0	32 - 47	<420	>5.5	>85%	=200		>90%		
AVERAGE	**25.6**	**74.8**	**6.0**	**45.0**	**415.2**	**5.2**	**88%**	**194.9**	**2.4**	**91%**	100%	57%
STDEV	1.0	5.3	0.4	1.0	9.5	0.5	5%	5.6	0.3	3%		
Min	23.7	65.5	5.2	43.1	398.0	4.4	89%	183.2	2.0	87%		
Max	27.3	84.1	6.7	46.6	426.7	6.1	96%	205.0	2.8	94%		
Pool 7 IPU	IPU Volume (mL)	IPU PYI	Potential Yield ($x10^{11}$)	PLS Ratio(%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	EDQM	CAT
N = 9	=28		>5.5	32 - 47	<420	>5.0	>85%	=200		>90%		
AVERAGE	**28.1**	**75.5**	**5.3**	**44.0**	**410.8**	**4.7**	**88%**	**197.4**	**2.2**	**94%**	100%	12%
STDEV	0.8	3.6	0.3	0.7	9.0	0.3	6%	4.6	0.1	2%		
Min	27.2	71.4	5.0	43.2	392.1	4.2	78%	187.6	1.9	91%		
Max	29.4	82.3	5.8	45.2	421.8	5.2	97%	205.4	2.5	97%		
Pool 7IPU > 60PYI	IPU Volume (mL)	IPU PYI	Potential Yield ($x10^{11}$)	PLS Ratio(%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	Volume (mL)	Yield ($x10^{11}$)	PLT Rcovery (%)	EDQM	CAT
N = 20	=28		>5.5	32 - 47	<420	>5.0	>85%	=200		>90%		
AVERAGE	**27,9**	**79.0**	**5,5**	**43,9**	**411,5**	**5,7**	**103%**	**197.4**	**2,6**	**93%**	100%	80%
STDEV	0.9	1.0	0.1	0.8	7.3	0.5	9%	4.2	0.3	4%		
Min	26.6	77.6	5.4	42.7	401.0	4.9	89%	191.5	2.2	84%		
Max	29.4	81.1	5.7	45.2	419.8	6.5	118%	203.4	3.0	99%		

Comparison of Pathogen-Reduced Platelets for 5 Days of Storage Treated With Two Different Commercially Available Pathogen-Inactivation Technologies

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BACKGROUND: Pathogen inactivation treatment (PIT) reduces the risk of bacterial, viral and parasite transmission through platelet transfusion, as well as the incidence of leukocyte-mediated transfusion reactions. However, it also may have an impact on platelet quality and efficacy. Comparison studies of different commercially available PIT technologies with platelets in platelet additive solution (PAS) have been conducted reporting significant differences between technologies with respect to platelet quality during the course of storage, but such studies with platelets in 100% plasma are lacking to date.

AIMS: Assessment of the impact of commercially available PIT technologies on the quality of apheresis platelets in 100% plasma until end of shelf life.

METHODS: Apheresis platelets in 100% plasma from voluntary donors with comparable attributes were collected with a Trima (Terumo BCT, U.S.A.), or an MCS+ (Haemonetics, U.S.A.) device and treated with either amotosalen/UVA (AS) (INTERCEPT Blood System, Cerus, U.S.A.) or Riboflavin/UVB (RB) (Mirasol PRT System, Terumo BCT) technology, followed by 5-day storage. Platelet count and pH (local standard QC testing) were monitored during the course of storage using a D3 hematology analyzer (Drew Scientific, U.S.A.) and a pH-102 device (Portlab, Russia) respectively. The twosample (unpaired) t-test was used to calculate statistical significance (a p-value of <0.05 was considered significant, a pvalue of <0.01 highly significant).

RESULTS: 30 platelet units per arm were collected with an average platelet count of $5.3 \times 10^{11} \pm 0.3$. There was no significant difference of donor characteristics with respect to sex (20% / 27% female), body weight in kg (83.3 ± 3.8 / 83.9 ± 4.9, P=0.598), total number of former apheresis donations (33.0 ± 14.2 / 32.6 ± 14.8, P=0.915) and donor platelet count ($220.7 \pm 12.2 / 223.2 \pm 11.8 \times 10^9$/L, P=0.423) between the study arms. Red blood cell (RBC) and white blood cell (WBC) counts of all platelet units were within specifications for PIT ($<4 \times 10^6$ RBC/mL and $<250 \times 10^6$ WBC/unit). The platelet loss during processing was higher in AS units (5.3%) compared to RB units (2.7%). Until day 3 of storage, there was no significant difference in platelet quality parameters between the study arms. Between day 3 and day 5 of storage, the average platelet count in the AS arm dropped to 98.4%. ± 7.7 of the post-treatment value (day 5 platelet count 5.0 ± 0.3), and in the RB arm to 84.2%. ± 15.7 (day 5 platelet count 4.2 ± 0.2) ($p<0.01$). Between day 3 and day 5 the average pH, as surrogate marker for metabolic activity, dropped in the AS arm from 7.2 ± 0.3 to 6.9 ± 0.5; and in the RB arm from 7.1 ± 0.1 to 6.5 ± 0.5 ($p<0.01$).

SUMMARY/CONCLUSIONS: The treatment of apheresis platelets with PIT technologies affected the *in vitro* quality differently, with potential impact on the clinical outcome. We recognized a highly significant reduction of platelet count and pH of RB-treated platelets compared to AS-treated platelets after day 3 of storage, leading to a reduction of storage time to maximum 3 days for RB platelets in 100% plasma in our blood center.

Amotosalen and UVA Treatment of *Bacillus Mobilis*, *Acinetobacter Seifertii*, *Staphylococcus Saprophyticus*, and *Leclercia Adecarboxylata* from a Contaminated Apheresis Platelet Unit

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BACKGROUND: The INTERCEPT® Blood System for Platelets uses a combination of amotosalen and UVA light to inactivate pathogens and leukocytes in platelet concentrates (PC). The system is in routine use in US and EU blood centers to treat either apheresis- or whole-blood derived platelets. In 2021, a septic transfusion reaction involving an INTERCEPT-treated apheresis PC was reported in Ohio, USA. Bacteria were isolated from the storage bag and identified as *Bacillus mobilis* (*BM*), *Acinetobacter seifertii* (*AS*) (previously identified as *Acinetobacter baumannii* complex), *Staphylococcus saprophyticus* (*SS*), and *Leclercia adecarboxylata* (*LA*). Only *SS* and *AS* were cultured from the patient. A subclinical leak near the platelet unit port suggested that environmental contamination of the unit occurred after pathogen reduction. *AS*, *SS* and *LA* are effectively inactivated by the INTERCEPT Blood System for Platelets alone and in combination (Fadeyi *et al*., Transfusion, 2020). This was the first published report of a *Bacillus mobilis* contamination and no inactivation data are available.

AIMS: The aim was to assess the inactivation of *BM* alone and in combination with *AS*, *SS* and *LA* in apheresis platelets using the INTERCEPT Blood System for Platelets.

METHODS: The bacterial strains were submitted to Charles River Laboratories for sequence typing using AccuGENX-ST. For the pathogen inactivation assessments, 335 mL of PC in 35% plasma and 65% PAS was inoculated with 3.4 mL of a log culture of an individual bacterial species or a 1:1:1:1 (volume) mixture of *BM*, *AS*, *SS* and *LA*. The contaminated platelet component was pathogen-inactivated utilizing the INTERCEPT Dual Storage Platelet Processing Set including the compound adsorption device (CAD), transferred into storage bags, and stored at 22°C under standard conditions. Samples were taken pre- and post-treatment, post-CAD, day 5, and day 7. Bacterial titer was measured by plating on *LB* agar.

RESULTS: AccuGENX-ST sequencing showed that the *AS* strain was clonally related to two previously reported *A. baumannii* complex bacteria implicated in TTI cases in California and North Carolina (Fadeyi *et al*., Transfusion, 2020; Fridey *et al*., Transfusion, 2020; Villa *et al*, Transfusion 2023). Both the *SS* and *LA* were clonally related to isolates involved in prior TTI cases in either Virginia or North Carolina, respectively. For the individual pathogen reduction assessment of a vegetative culture of *BM*, 3.6 ± 0.1 log CFU/mL was inactivated with no detectable bacteria observed out to 7-days post-collection. For the combination assessment, inactivation of the combined mixture of *BM* (vegetative culture) , *AS*, *SS* and *LA* were observed at >7.0 ± 0.0 log CFU/mL with no detectable bacteria post-treatment out to 7-days. The calculated inactivation for each bacteria in this combined inactivation was 3.0 ± 0.0 log cfu/mL, 7.5 ± 0.0 log cfu/mL, 7.4 ± 0.1 log cfu/mL and 6.5 ± 0.1 log cfu/mL for *BM*, *AS*, *SS*, and *LA*, respectively.

SUMMARY/CONCLUSIONS: Isolates of *AS*, *SS* and *LA* from the Ohio case were clonally related to bacteria involved in TTIs across the United States suggesting a possible common origin, as previously described (Villa *et al*, 2023). We demonstrate that amotosalen/UVA treatment can effectively inactivate multiple bacterial species in a single unit, including *BM*, *AS*, *SS*, and *LA* alone and in combination. Further studies are needed to understand the mechanism of contamination of units after treatment during the storage period.

Successful Inactivation of Pathogenic Bacterial Strains in Double-Dose Pooled Buffy Coat Platelet Using Amotosalen/UVA Pathogen Reduction Treatment

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BACKGROUND: Platelets components provide ideal conditions for bacterial proliferation which can lead to septic transfusion reactions and significant morbidity and even mortality for vulnerable recipients. Blood establishments worldwide mitigate this risk using different strategies including bacterial screening of platelets and the use of pathogen-reduction technology. Here we describe successful bioburden reduction of pathogenic strains in whole blood derived 7 buffy coat (BC) double-dose pools (prepared using TerumoBCT TACSI® System) through use of the Cerus INTERCEPT™ Blood System (IBS).

AIMS: To demonstrate the ability of the IBS to successfully reduce pathogenic bacteria level to 'Sterile at out-date' under conditions of normal operation. Eight bacterial strains (WHO and IBTS) were used (**Table 1**).

METHODS: A paired case-control study, comparing bio-burden reduction of pathogenic bacteria in pathogen reduced and untreated (control) platelets, was performed. Successful pathogen reduction was indicated by 'Sterility at out-date'. Estimating initial inoculating dose is difficult due to mitigation and production steps taken to reduce bacterial contamination; a 'high' likely initial dose of 500 CFU per platelet dose was used. BCs were separated from whole blood by hard-spin centrifugation on Day 1. Seven ABO-identical BCs were then pooled with 280 ml of Platelet Additive Solution (Macopharma SSP+) using TerumoBCT TACSI system, producing a double-dose (DD) pool. Two DD pools were then combined and mixed; sample was taken to confirm Sterility (8ml in each of BPA and BPN bottles (Biomerieux BACT/ALERT (BTA) 3D)). Combined DD pool (14-BCs) was inoculated with 2,000 CFU (500 CFU/dose). After 2-hours rest, the combined DD pool was split in two identical DD pools. Day 1 Pre-PR samples were taken from each DD pool for CFU and BTA 3D. One DD underwent pathogen-reduction using IBS with Dual Storage (DS) sets; the second DD remained untreated as control. On Day 2 after removal of amotosalen (CAD 14-15 hours), the PR DD was split into two identical single-dose pools; control DD pool was split into two equal untreated single-dose pools (using DS bags). Samples were taken from each SD pool for CFU and BTA 3D. All platelet pools were agitated at 22°C until expiry. Samples were taken on Day 8 (out-date) for CFU and BTA 3D. All BPA/BPN bottles were incubated on BTA 3D to positivity or 7-days. Strain confirmation was performed by MALDI-TOF (Vitex MS, Biomerieux). This was repeated for all eight strains.

RESULTS: All strains of bacteria proliferated in control pools, increasing in concentration over shelf-life. 7 of 8 selected strains did not grow in pathogen-reduced pools, and were 'sterile at outdate'. *Bacillus cereus* was specifically selected as a spore-producing organism; PR had no effect on the ability of *B. cereus* to grow in pools. This is a known limitation of PR technology. Identification of all bacterial strains isolated from positive bottles was as expected.

SUMMARY/CONCLUSIONS: IBS Pathogen reduction technology performed as expected for all eight bacterial strains used, for what we believe to be realistic inoculating doses.

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Table 1: Bacterial Strains

Organism	Strain	Source	Sterile at Outdate
Staphylococcus epidermidis	IBTS-567/18	IBTS	Y
Klebsiella pneumoniae	PEI-B-P-08	WHO	Y
Staphylococcus aureus	IBTS-073/21	IBTS	Y
Serratia marcescens	IBTS-374/20	IBTS	Y
Enterobacter cloacae	PEI-B-P-43	WHO	Y
Proteus mirabilis	PEI-B-P-55	WHO	Y
Streptococcus dysgalactiae	PEI-B-P-71	WHO	Y
Bacillus cereus	PEI-B-P-57	WHO	N

Therapeutic Comparative Study of Whole Blood Derived Platelet Concentrates Treated With Amotosalen-UVA Pathogen Reduction Technique Versus Irradiated In Patients With Hematological Pathology

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BACKGROUND: Different types of platelet concentrates (PC) are currently available for transfusion, such as those that have undergone irradiation (IRPC) or pathogen reduction techniques (PRPC). Knowing its variability both from an analytical point of view and its clinical effectiveness is necessary.

AIMS: To know the clinical-analytical differences between PRPC and IRPC prepared from whole blood in adult patients with different onco-haematological conditions.

METHODS: After high-speed whole blood centrifugation, Buffy-coats (BC) were obtained. In the case of IRPC, 4 BCs were pooled together with 300 mL of PAS-E and centrifuged with the TACSI system (Terumo®), 12 hours later PCs were irradiated. The PRPC were prepared by mixing 8 BCs and 280 mL of PAS-E. This mixture was centrifuged, and a “mega” PC was obtained, which was inactivated with a pathogen reduction technology based on amotosalen and UVA (INTERCEPT™ Blood System) after which it was split into two adult doses. The selected patients with oncohaematological conditions belonged to a single hospital. In the first period, IRPC were transfused exclusively and in the second period, PRCP were transfused. The following clinical-analytical data were recognized: sex, date of birth, weight, height, blood group, underlying pathology, type of treatment, transplantation and type, haemorrhagic risk factors, indication for transplantation, type of platelet transfusion indication (prophylactic vs therapeutic), platelet count before and after transfusion, PC platelet content, the existence of previous refractoriness, adverse transfusion reactions, the existence of bleeding, bleeding severity, and location, transfusion of packed red blood cells (RBCC), exitus, and its cause. The patient's platelet counts were taken before and after transfusion at 1 hour and 24 hours, and the CCI was calculated. For the analysis, the chi-square statistic was used for categorical variables and Student's t-test for continuous variables with the SPSS software.

RESULTS: We share the preliminary results of this study. We have studied 64 transfusion episodes with 31 IRPCs and 33 PRPCs, with a similar distribution of sex, age, and body surface area between both groups. Also, there are no significant differences in the type of indication for platelet transfusion, previous bleeding risk factors, subsequent adverse reactions, post-transfusion bleeding, or number of transfused RBCC. On the other hand, a significant difference is observed between the groups (IRPC vs PRCP) in: initial diagnosis (more CART and AML in IRCP, more aplastic anaemia and MDS in PRCP), treatment phase (more transplantations in PRPC; more CART and relapse in IRPC), the source of progenitors (more bone marrow in PRPC), death (more in IRPC), and higher CCI, posttransfusion platelet count and platelet content in the product in IRCP (9697 vs 4420; 31225/µL vs 19787/µL and 2.86×10^{11} vs 2.42×10^{11}).

SUMMARY/CONCLUSIONS: No definitive conclusions can be drawn from the preliminary results shown here. It is important to highlight the absence of differences in adverse reactions, post-transfusion bleeding or the number of red blood cell concentrates transfused, which may lead to considering a similar clinical effectiveness for the intended use of PC.

Optimization and *In-Vitro* Qualification of Pathogen Reduced Double Dose Pooled Platelets of Seven Buffy Coats Throughout 8 Days of Storage

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BACKGROUND: Platelets carry a greater risk of bacterial contamination, compared to other blood components, due to their storage at room temperature. Many blood establishments worldwide have successfully implemented pathogen reduction technologies, which provides an alternative approach to traditional bacterial culture methods by inactivation of a broad range of potentially harmful agents in blood products and, consequently reducing the risk of transfusion-transmitted infections. Here we describe, for the first time, the *in-vitro* platelet quality assessment of whole blood derived double dose pools, prepared using 7 buffy coats pooled on the Terumo Automated Centrifuge & Separator Integration (TACSI®) System, and pathogen reduced (PR) with the INTERCEPT™ Blood System (IBS), throughout 8 days of storage.

AIMS: The primary aim was to optimize and validate the preparation and storage of double dose pools of 7 buffy coats, PR with the IBS and verify that they comply with the EDQM Guidelines 21st Edition (European Directorate for the Quality of Medicines & HealthCare). Secondly, to investigate the impact of the IBS photochemical process on the quality and function of pooled platelets compared to conventional untreated platelets, throughout storage.

METHODS: A paired case-control study comparing the biochemical and functional differences detected between PR and untreated platelet was carried out. Buffy coats (BC) (n=70), were separated from whole blood by hard-spin centrifugation. Seven ABO-identical BCs were then pooled with 280 ml of Platelet Additive Solution (SSP+), and double dose (DD) pools (n=10) were produced using the TACSI® System. Subsequently two DD pools were combined and split to generate 10 paired DD platelet units. Platelet units were treated with either the IBS (n=5), or remained untreated controls (n=5). All platelet units were then split into two equal single-dose units and stored in the INTERCEPT storage bags for 8 days at 22°C with agitation. *In-vitro* quality and function of platelets were assessed throughout storage with routine quality control tests and advanced flow-cytometry at varying time-points (baseline, day 2, day 6 and at expiry on day 8).

RESULTS: All quality parameters tested throughout the optimization and process validation met the IBS processing requirements to undergo treatment using the Dual Storage kit. The final units were in compliance with the EDQM specifications (**Table 1**). Platelet concentration significantly dropped in PR from day 2 storage onwards ($p<0.05$), while remained constant in the controls (**Table 2**). However, all platelet units met the required specification for platelet concentration of on all days tested. No aggregates and good swirling were observed for all units throughout 8 days of storage, with higher swirling scores on day 2 for PR platelets. MPV values were stable and comparable and minimal difference was observed for pCO_2 and pO_2. All units had pH values of ≥6.4 with sufficient glucose reserves at the end of storage; however, higher glucose values were detected in IBS treated platelets (**Table 2**). CD62P expression and Phosphatidylserine (PS) exposure significantly increased over storage for both treated and untreated platelets indicating comparable levels of storage lesion and apoptosis, (**Table 2**). Platelet stimulation by the thrombin agonist TRAP and PS agonist calcium resulted in high levels of responsiveness in both groups at each time point.

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(>80% CD62P expression and >99% PS exposure; **Table 2**), indicating that PR platelets are capable of haemostatic response and pro-coagulant activity beyond 7 days of storage.

SUMMARY/CONCLUSIONS: This study validated an optimal process for the production of 7 buffy coat-double-dose pooled platelets suitable for IBS treatment, and provides evidence that *in vitro* platelet quality and function is adequately maintained following IBS treatment and storage in SSP+ for at least 7 days.

Table 1: Optimization and Process Validation of DD Pools of 7 Buffy Coats Stored in 280 ml SSP+ and Pathogen Reduced With IBS

	DD INTERCEPT input requirement/ EDQM specification	Optimization of DD POOL (n=10)	Final INTERCEPT treated platelets (n=24 single doses)
Volume (ml)	375 - 420 (DD) ≥ 175ml (single dose)	414 ± 4	191 ± 6
Platelet Content (x 10^9/pool)	> 450 DD ≥200 (single dose)	558 ± 92	243 ± 26
Plasma ratio (%)	32 – 47%	40 ± 0.8	N/A
RBC contamination (x 10^9/l)	<4	Visually Absent	N/A
Platelet recovery (%)	>80	90 ± 1.6	N/A
Platelet Concentration (x 60 x 10^9)	≥ 35 ml	46 ± 7	48 ± 5
Leucocyte content (x 10^6/pool)	< 1 per split pool	0.11 ± 0.05	0.03 ± 0.0
Glucose (end of shelf life) (LoQ)	Above Limit of Quantification	N/A	1.9 ± 0.9
pH (end of shelf-life) (kPa)	≥ 6.4	6.9 ± 0.1	7.19 ± 0
Swirling	Score 1-3	2 ± 0.5	3
Aggregates	Score ≤1	0	0
Microbial growth	Negative	N/A	Negative

Values are reported as mean and standard deviation (SD)

Table 2: Pathogen Reduced and Conventional Untreated Platelet Quality and Functional Parameters Throughout 8 Days of Storage

Platelet parameter	Day of storage	PR platelet		Untreated platelet (control)	
		Mean	p-values	Mean	p-values
PLT Concentration (10^9 cells/L)	Baseline	1282		1272	
	2	1230		1277	
	6	1176		1285	
	8	1143	*0.017	1238	0.323
MPV (fL)	Baseline	10.1		10.2	
	2	10.2		10.1	
	6	10.1		10.1	
	8	10.1	0.824	10.0	0.716

* Denotes Statistical significance over storage following Friedman test statistical analysis of variance

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Table 2 Continued: Pathogen Reduced and Conventional Untreated Platelet Quality and Functional Parameters Throughout 8 Days of Storage

Platelet parameter	Day of storage	PR platelet		Untreated platelet (control)	
		Mean	p-values	Mean	p-values
Glucose (mmol/L)	Baseline	9.0		9.0	
	2	8.1		7.2	
	6	4.6		4.0	
	8	2.2	*0.002	1.7	*0.002
pH (37°C) (kPa)	Baseline	7.1		7.1	
	2	7.0		7.1	
	6	7.1		7.2	
	8	7.0	*0.029	7.1	*0.037
pCO_2 (37°C) (kPa)	Baseline	4.3		4.1	
	2	4.0		3.9	
	6	2.0		2.2	
	8	1.9	*0.003	2.1	*0.006
pO_2 (37°C) (kPa)	Baseline	15.6		16.4	
	2	17.3		21.6	
	6	21.8		21.2	
	8	19.9	*0.043	19.0	0.290
CD62P expression (%) Baseline	Baseline	27.1		29.1	
	2	30.5		32.9	
	6	42.2		39.4	
	8	47.1	*0.002	44.3	*0.002
Responsiveness to TRAP) (%) Baseline	Baseline	83.5		87.9	
	2	83.9		89.2	
	6	83.1		87.9	
	8	86.2	0.564	89.1	0.896
PS exposure (%)	Baseline	2.2		2.5	
	2	2.6		2.5	
	6	8.3		6.7	
	8	11.1	*0.006	8.4	*0.004
Agonist induced-PS exposure (%)	Baseline	99.4		99.3	
	2	99.5		99.5	
	6	99.7		99.8	
	8	99.6	0.137	99.8	*0.017

* Denotes Statistical significance over storage following Friedman test statistical analysis of variance

Comparative *In Vitro* Study of Room Temperature and Cold Stored Double Dose Platelets Pathogen-Reduced With Amotosalen and UVA Light

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BACKGROUND: Platelet concentrates (PC)are normally stored at 22°C for up to 5 days and extended storage up to 7 days can be applied only if bacterial detection or a pathogen reduction treatment is performed after production of PC. The current needs for platelet transfusions are changing and nowadays more platelets are given to patients who are actively bleeding and since cold-stored platelets are more hemostatically effective and potentially longer shelf life. There is an enormous interest in cold-stored platelets but before this product is used in routine or for specific patients, investigation of *in vitro* storage characteristics and *in vivo* transfusion effects is required

AIMS: This *in vitro* study compares room temperature (RT) and cold-stored double-dose platelets (DD PLTs) treated with Amotosalen and UVA light over 21 days. The objective is to assess biochemical and functional properties of RT and coldstored DD PLTs. Parameters like volume, PLT content, pH, swirling, pO_2, pCO_2, HCO_3^-, LDH, and glucose are evaluated. DD-PCs are prepared from 8 ABO-matched whole blood-derived buffy-coat units, pooled with platelet additive solution. Four storage conditions are studied: C-PC at 22°C or 4°C, and PI-PC at 22°C or 4°C. Results from 3 replicates show stable pH, moderate decreases in values, slightly increased LDH concentrations, and maintained glucose reserves until Day 7, especially at 4°C. Clinical studies of cold-stored platelets in bleeding patients are essential to assess their effectiveness in minimizing time to hemostasis and rebleeding events. Further tests, including CD62P measurement and ROTEM analysis, are ongoing, and additional replicates are needed for a comprehensive understanding

METHODS: Double dose platelet concentrates (DD-PC) are prepared from 8 ABO-matched whole blood-derived (WB) buffy-coat units (BC) . The buffy-coats employed in this study are buffy-coats not used for the routine PC production because of the donor low platelet count. The 8 BC are pooled with 280 mL of platelet additive solution (PAS, Intersol) using manual pooling method. For each replicate, two ABO-identical double-dose platelet concentrates free of aggregates, are mixed and divided into two DDPC. Each replicate will include therefore 4 arms: Study arms 1,2: CONTROL PC (C- PC) stored at 22°C in a platelet agitator or at 4°C, without agitation. Study arm 3, 4: pathogen inactivated PC (PI – PC) stored either at 22°C in a platelet agitator or at 4°C, without agitation. All 4 types of PC will be stored in platelet containers from INTERCEPT DS kit up to 21 days. Samples during storage are taken on Days 2, 5, 7, 14 and 21 for evaluation of *in vitro* platelet function and metabolism.

RESULTS: Preliminary results from 3 replicates have been analyzed for metabolic parameters. From this initial data set, we have observed that pH is maintained well during the storage period of 21 days even if values are moderately decreased over storage. LDH concentrations are slightly increased, and glucose reserves are maintained until Day 7, especially in PC stored at 4°C.

SUMMARY/CONCLUSIONS: Even if the data set is limited and more replicates and further tests are required (CD62P measurement by flow cytometry and ROTEM analysis), our study provides additional information regarding *in vitro* parameters of PC stored at 4°C. It's clear that clinical studies of cold-stored platelets in acutely bleeding patients are needed to determine whether refrigerated platelets will minimize time to hemostasis and rebleeding events.

Introduction of 7-Day Amotosalen/UVA Pathogen Reduced Platelets In Honduras: Impact on Platelet Availability In a Lower Middle Income Country

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BACKGROUND: The Honduran Red Cross (HRC) produces and distributes ~70% of the platelet concentrates (PCs) transfused in Honduras, a lower middle income country (LMIC) of approximately 10 million people in Latin America. Honduras became the first LMIC to adopt amotosalen/UVA pathogen reduced (PR) PCs as the standard of care in 2018. HRC produces platelet rich plasma (PRP) PCs derived from whole blood (WB). Prior to 2018 all PCs were screened for bacterial contamination (BacT/Alert) and issued as single, non-pooled, donor PRPs (SD-PRP) with a 5-day shelf-life. The dosing regimen was based on patient weight. The transition to PR PCs was accompanied by a shift to pools of 6-PRPs with a standardized dose of $\geq 3.0 \times 10^{11}$, the elimination of bacterial culture screening, and an extension of PC shelf-life to 7-days.

AIMS: To describe PC production and distribution trends in Honduras over 8 years before and after introduction of PR, standardized pooling, and 7-day shelf-life.

METHODS: Annual PC production and distribution data, and WB collection data were retrospectively extracted from HRC records for 2015-2023 and analyzed in 2 periods. Period 1 (P1) included 3 years of SD-PRP doses (2015-17) and the transition year (2018). Period 2 (P2) included 5 years of pooled PR PC doses (2019-23). PC doses were standardized to an equivalent adult dose for both periods: SD-PRP doses in P1 used a 1 SD-PRP per 10 kg dosing formula and a mean adult (male and female) weight estimate of 63 kg; pooled PR PC doses in P2 included 6 SD-PRPs. Descriptive statistics were calculated for 2-period comparisons and multi-year trends. Population data were obtained from the National Institute of Statistics.

RESULTS: HRC produced 10% more PC doses per year on average in P1 compared to P2. Standardization with 7-day shelf-life enabled the distribution of 58% more PC doses per year on average in P2. The mean annual distribution of produced PC doses increased from 64.9% in P1 to 98.9% in P2 (**Table**). A total of 27,635 adult PC doses were produced by HRC between 2015-23. Of these, 24,579 (88.9%) were distributed to 16 of 18 regions in Honduras (2 regions did not report any PC use in either period). Two regions accounting for ~40% of the population consumed 96% of PC doses in P1 and 88.3% in P2. PC distributions increased in 15/16 regions and declined in 1 region. Six of 16 regions (37.5%) received no or <1 PC dose per year on average in P1; all 16 regions received at least 1 PC dose per year in P2. WB collections increased by ~40%, driven in part by ~13.7% population growth.

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Pooled or 6-pool equivalent PC doses	Year	Produced	Distributed	Est. Waste (%)
P1: SD-PRP + Transition	2015	2,854	1,844	35.4%
	2016	3,283	2,223	32.3%
	2017	2,91	2,166	25.6%
	2018	2,818	2,752	2.4%
P2: Pooled PR PC	2019	3,316	3,278	1.1%
	2020	2,826	2,791	1.2%
	2021	3,914	3,884	0.8%
	2022	3,364	3,33	1.0%
	2023	3,164	3,126	1.2%

SUMMARY/CONCLUSIONS: Standardized pooling, PR and shelf-life extension to 7-days allowed HRC to increase distribution of PC doses without requiring additional WB donations. PC distribution is concentrated in urban areas, but increased production permitted additional distribution in some rural areas. Access to PC transfusion remains limited in Honduras (<1 PC dose per 1,000 population); however, the conversion to pooled PR PCs illustrates the potential to sustainably expand PC availability in an LMIC through optimization and standardization. Additional research is needed to describe the cost and clinical use of PCs in Honduras.

Comparison of the Quality Parameters of Irradiated vs Pathogen-Reduced Platelet Products

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BACKGROUND: Currently, different platelet products are produced in Blood Establishments. Starting from whole blood (WB), after preparing the platelet pool, obtained from Buffy-coat (BC), and before releasing it to hospitals, it can be irradiated (PCIR) or treated with pathogen reduction techniques (PCPR). Due to this diversity, it is necessary to know the characteristics of these products because those parameters may influence on the clinical response.

AIMS: To know the different attributes of PCIR and PCPR, such as platelet count/microL, total platelet count/unit, platelet concentration, volume, swirling, and days of storage at the time of their distribution.

METHODS: A total of 523 PCIR and 311 PCPR have been analysed. In the first period, between May and July 2023, the PCIR were produced, and in the second period, between October 2023 and January 2024, the PCPR. BCs were obtained after a fast centrifugation of the WB. PCIRs were obtained by mixing 4 BC with 300 mL of PAS-E (Grifols®) and TACSI automated system (Terumo®) was used. The day after their preparation platelets were irradiated and analysed. PCPR were created by mixing 8 BC and 280 mL of PAS-E (Macopharma®), this prepool was centrifugated at 1650 RPM (G: 850), acceleration: 3, brake: 3, and time: 7 minutes. Then, platelets were desplasmatized using Macopress Smarter fractionators (Macopharma®), after that, platelets were transferred to the inactivation kits (Cerus®) and treated with amotosalen and UVA. Amotosalen was removed in the compound adsorption device for 14 hours, and platelets were split in two products with the same volume. To obtain weight an electronic balance was used, platelet count was determined using Coulter BC-3600 (Mindray®), and the presence of swirling was classified as 0: absent, 1 slight, 2: moderate, 3: strong.

A statistical study was carried out using the SPSS program. This study consisted of a descriptive study of the two types of platelet concentrates (mean, median, range, percentiles, and standard deviation), as well as a comparison of the continuous and categorical variables with t Student and Fisher test respectively, a *p* lower than 0.05 was considered as significant.

RESULTS: They are shown in the attached **Tables**.

CONCLUSIONS: Statistically significant differences were shown in volume, platelet count and concentration and, in the number of days of storage. Despite that, both PCIR and PCPR met all the requirements of the Council of Europe. These differences may not have an influence on clinical response, because of that, a study about their therapeutic effect will be conducted. Differences in the day of the distribution are significant. PCPR can be delivered sooner and, also, released until day 7.

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Table 1: Descriptive Study PCIR and PCPR

		N	Mean ± Standard Deviation	Median	Min	Max	Range	*p*
Volume (mL)	PCIR	523	364.60 ± 12.49	364.00	300.00	421.00	121.00	<0.001
	PCPR	311	184.38 ± 10.11	184.00	155.00	286.00	131.00	<0.001
Nº platelets x10^{11} /unit	PCIR	523	2.93 ± 0.41	2.91	2.00	4.07	2.07	<0.001
	PCPR	311	2.56 ± 0.29	2.54	1.87	3.58	1.71	<0.001
Platelets x10^{9}/mL	PCIR	523	0.8 ± 0.1	0.7	0.5	1.1	0.6	<0.001
	PCPR	311	1.3 ± 0.15	1.3	1.0	1.7	0.7	<0.001
Platelet storage (days)	PCIR	523	3.14 ± 0.98	3	2	5	3	<0.001
	PCPR	311	2.84 ± 1.02	2	2	6	4	<0.001

Table 2: Study of Categorical Variables, Swirling

	PCIR (%)	PCPR (%)	p*
<=2	3 (0.6)	0 (0)	0.298
3	520 (99.4)	311 (100)	
Total	523	311	834

*Fisher test

Amotosalen/UVA Treatment of Platelet and Plasma Components Using the INTERCEPT Blood Systems to Inactivate WHO Reference Bacterial Strains

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BACKGROUND: The INTERCEPT® Blood Systems (IBS) for platelets and plasma utilize amotosalen and UVA light to inactivate a wide range of pathogens and leukocytes in platelet concentrates (PC) and plasma. IBS for Platelets is routinely used for the treatment of apheresis and whole blood (WB) derived platelets in Europe, and in the US for the treatment of apheresis platelets (TRIMA® in 100% plasma or AMICUS® for 65% PAS-C/35% plasma). IBS for Plasma is available both in Europe and the US. The World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) in association with the Paul-Ehrlich-Institut (PEI) approved an extended panel of bacterial strains to evaluate methods for improving the microbial safety of blood components (Spindler-Raffel *et al*, 2015).

AIMS: The aim of this study was to evaluate the inactivation of WHO reference (PEI) bacterial strains in platelet and plasma components using the INTERCEPT® Blood Systems.

METHODS: Apheresis PC collected in 100% plasma or 65% Platelet additive solution (PAS-C)/35% plasma were pooled into individual units of 420 mL with platelet doses of 4.0 to 5.0 × 10^{11} and 4.0 to 7.9 × 10^{11} respectively (IBS for Platelets – Dual Storage (DS) Processing Set). Human plasma donations were collected and pooled to yield individual units of ~650 mL (IBS for Plasma). Four replicates per platelet matrix were performed for 3 PEI strains of transfusion-relevant bacteria, as well as for *P. fluorescens* in plasma, with each replicate consisting of one component spiked with a single PEI strain. The contaminated PC and plasma units were then treated with the IBS for platelets and plasma, respectively. Samples were taken pre-UVA illumination (~5 mL) and post-UVA illumination prior to CAD treatment (~50 mL) and were analyzed for bacterial titer by plating on appropriate media (100µL–10mL/plate) and incubating for at least 24 hours.

RESULTS: INTERCEPT treatment of platelet and plasma units spiked with bacteria from the PEI/WHO strains (**Table 1**) led to robust bacterial inactivation (**Table 1**).

SUMMARY/CONCLUSIONS: The INTERCEPT Blood System for Plasma consistently inactivated high titers of *P. fluorescens*. The INTERCEPT Blood System for Platelets efficiently inactivated *P. fluorescens*, *E. cloacae* and *B. thuringiensis*. The data demonstrate that IBS robustly inactivates the tested WHO standardized bacteria strains associated with transfusion transmitted bacterial infections (TTBI).

References Spindler-Raffel *et al*,. 2015 Enlargement of the WHO international repository for platelet transfusion-relevant bacteria reference strains. *Vox Sang*, 112: 713-722.

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Table 1: Bacterial Inactivation Using Amotosalen/UVA Treatment for Human Plasma and Platelet Concentrates in 100% Plasma (PLS) or in 65% PAS-C/35% Plasma (PLS)

Bacteria (Strain)	Matrix	Log Reduction (Log cfu/mL)
Pseudomonas fluorescens PEI-B-P-77	PC (100% PLS)	6.6 ± 1.4
Pseudomonas fluorescens PEI-B-P-77	PC (65% PAS/35% PLS)	7.8 ± 0.1*
Pseudomonas fluorescens PEI-B-P-77	Plasma	7.2 ± 0.8
Enterobacter cloacae PEI-B-P-43	PC (100% PLS)	6.5 ± 0.1
Enterobacter cloacae PEI-B-P-43	PC (65% PAS/35% PLS)	6.7 ± 0.1*
Bacillus thuringensis PEI-B-P-07	PC (100% PLS)	5.7 ± 0.1
Bacillus thuringensis PEI-B-P-07	PC (65% PAS/35% PLS)	5.5 ± 0.1*

*No residual bacteria were detected post UVA treatment. The limit of detection is 1 cfu/50 mL.

Safety of Amotosalen/UVA Platelets and Plasma Transfused In Routine Clinical Use: Real World Evidence From 2 Large European Transfusion Medicine Centers, 2019-22

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BACKGROUND: Pathogen reduced (PR) platelet (PLT) and plasma (PLS) components were approved in Europe in 2002 and 2006, respectively. Cerus, the manufacturer of the amotosalen/UVA technology (INTERCEPT® Blood System) conducts voluntary periodic hemovigilance (HV) studies with centers using the technology to collect real world evidence (RWE) on the safety of INTERCEPT treated components transfused in routine clinical use. Previous sponsored HV studies collected safety data on 21,548 INTERCEPT PLTs in 4,765 patients and 57,428 INTERCEPT PLS in 9,813 patients in 11 countries between 2003-16. A new round of data collection began in 2019. Data collected through November 2022 are presented.

AIMS: To document the nature, frequency and severity of transfusion reactions (TRs) in patients transfused with INTERCEPT PLTs and/or PLS in routine clinical practice and compare these findings with historical data.

METHODS: Two hospitals in Graz, Austria and Warsaw, Poland participated in this observational, non-interventional, singlearm study. Data related to the use of INTERCEPT PLTs and PLS were collected prospectively from routine hospital and blood bank data systems for all patients transfused in selected wards during defined surveillance periods. De-identified patient data were stratified by sex, age and clinical diagnosis. TRs were defined according to ISBT terms and identified by physicians using hospital reporting systems. Descriptive statistics were calculated for each site.

RESULTS: A total of 2,340 PLT and 1,181 PLS components were transfused to 299 and 59 patients, respectively. Apheresis accounted for 44% of PLTs transfused in Graz and 88.1% in Warsaw. All PLS components in Graz were from apheresis; >97% of PLS in Warsaw were derived from whole blood. All PLTs in Graz and 60% of PLTs in Warsaw were suspended in platelet additive solution (SSP+); the remainder of PLTs in Warsaw were stored in 100% plasma. All PLTs were approved for 7-day storage. Both sites transfused >75% of PLTs on days 2-5 post-collection; ~3-4% of PLTs were transfused on day 7. Approximately 1.4% of PLTs in Warsaw were cryopreserved and transfused after day 7. Per patient PLT utilization was similar in both sites (mean: 8, range: 1-58). Five PLT TRs were reported (2 febrile non-hemolytic TRs [FNHTR] in Graz; 1 FNHTR and 2 allergic TRs in Warsaw). The per PLT TR rate was 0.21% for both sites. Two PLS TRs (allergic and unclassified) were reported in Warsaw (0.17% per PLS rate). All TRs were non-serious and moderate in severity; all patients recovered without complications. Rates were comparable to historical rates for PR and non-PR components at the participating hospitals and lower than rates (~1%) observed in prior HV studies.

SUMMARY/CONCLUSIONS: Cross-sectional HV studies allow hospitals and medical device manufacturers to reaffirm safety profiles with RWE. Cerus aims to complete the study in 2024 with an additional ~2,000 PLT and/or PLS units (total >5,000) in the final dataset.

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	Site	Graz	Warsaw	Total
Platelets	Subjects	134	165	299
	Units	1,054	1,286	2,34
	TRs	2	3	5
	%TR / units	0.19%	0.23%	0.21%
Plasma	Subjects	7	52	59
	Units	462	719	1,181
	TRs	0	2	2
	%TR / units	0.00%	0.28%	0.17%

Optimization of Pathogen-Reduced Therapeutic Plasma and Platelet Units for Pediatric Use – A 5-Year Experience

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BACKGROUND: Pediatric patients have different requirements for plasma and platelet units with respect to component volume and platelet dose. In a clinical ward, splitting of adult doses to meet pediatric needs is not possible. Furthermore, pediatric patients are vulnerable patients requiring high blood safety standards. To facilitate pediatric transfusion and increase safety, pathogen-reduced pediatric platelet and plasma units (pooled plasma to increase standardization) were produced and optimized for pediatrician need since 2019 in the Warsaw Regional Blood Transfusion Center, mainly for the Monument Child Health Center, the Mother and Child Institute and the University Clinical Center in Warsaw. Platelet and plasma quantities and dose sizes for children, infants and neonates were adapted according to transfusing pediatricians (TP) needs, with latest adaptions in 2023.

AIMS: Production of pathogen-reduced pediatric therapeutic plasma (PTPLS) and platelet (PTPC) units and adaptation to TP needs.

METHODS: Plasma was produced from whole-blood donations with the buffy coat method using automated Compomat G5 presses (Fresenius-Kabi, Germany). Five ABO-compatible whole-blood derived single donor plasma units (≥ 270 ml) were pooled using the DONOpack plasma pooling set (LMB Technologies, Germany). Subsequently the pool (≥1260 mL) was split into 2 equal minipools (≥630 mL) which were treated with amotosalen/UVA pathogen inactivation (INTERCEPT Blood System, Cerus, U.S.A.). Each minipool was split into 6 PTPLS units (between 50 and 280 mL) into plasma storage bags (from INTERCEPT plasma processing sets), the final product was frozen within 8 h of collection (FFP) with a plasma freezer (HOF, Germany). Platelets in 65% PAS (SSP+, Macopharma, France) and 35% plasma were collected by apheresis ($4.3 \pm 0.4 \times 10^{11}$ platelets, 266.4±4.4 mL volume) with an Amicus device (Fresenius-Kabi). After 2 h resting time, platelets were treated with amtosalen/UVA (INTERCEPT Blood System, Cerus). The units were split into PTPC units according to clinician orders (15-150 mL) in pediatric 150 mL platelet storage bags (Ravimed, Poland) and incubated at 20-22°C under continuous agitation.

RESULTS: Initially we started in 2019 (demand 1049 PTPLS units) with a split ratio of 2x50 mL, 1x80 mL, 2x100 mL, and 1x 250 mL of plasma. In 2020, the demand increased to 1362 PTPLS units. The split ratio was adapted based on TP feedback to 2x50 mL, 3x100 mL and 1x 230 mL. The demand dropped in 2021 back to 1049 units, likely due to a COVID-19 pandemic related reduction of routine procedures. The third TP-feedback based adaption lead to a split ratio of 3x50 mL, 2x100 mL and 1x280 mL. In 2022 the demand increased to 2697 released PTPLS units, likely due restart of routine procedures and additional pediatric wards using our pediatric products. The last adaption was conducted in 2023 to a split ratio of 5x 100 mL and 1x 130 mL for PTPLS. The demand for PTPLS units dropped to 2007 units 2023. PTPC units were split on demand, 5 mL/kg of body weight (in average 8.1×10^{9} platelets per kg). The demand for pediatric PTPC units increased from 3480 (2019) to 3779 (2020). In 2021-2023 it was stable at 4346±20 units annually.

SUMMARY/CONCLUSIONS: The demand for pathogen-reduced pediatric plasma and platelet units increased over a 5-year period by increasing adoption of regional hospitals. The ideal unit size of PTPLS to meet clinical needs is, after the 4th adaption by pediatricians, 100 mL.

Development of a Next Generation Illuminator for Photochemical Inactivation of a Broad Spectrum of Pathogens In Platelet Concentrates and Plasma

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BACKGROUND: The INTERCEPT® Blood System for Platelets and Plasma uses amotosalen and ultraviolet A (UVA) light to inactivate a broad spectrum of pathogens and leukocytes in donor platelet concentrates (PC) and plasma, respectively. The current commercial illuminator (INT100) uses fluorescent bulbs to deliver a controlled dose of UVA light. In recent years, Cerus has developed a new LED-based illuminator (INT200) as a planned replacement for the INT100. There is no change to the intended use of the Illuminator.

AIMS: The objective of these studies was to compare the performance of the INT200 Illuminator to the INT100 Illuminator through the evaluation of pathogen inactivation levels achieved in PC and plasma.

METHODS: Two-arm pool and split studies were performed with apheresis PC (35% plasma/65% PAS-3 and 100% plasma) and with plasma. Pooled PC or plasma were spiked with the pathogen of interest and split into two identical units. The contaminated PC and plasma components were treated with the INTERCEPT processing sets for platelets or plasma, respectively. One unit was illuminated using the INT100 Illuminator and the second unit was illuminated using the INT200 Illuminator.

RESULTS: **Tables 1 and 2** show the inactivation levels achieved with amotosalen using the INT100 and INT200 Illuminators, as indicated by the log reduction factors (LRFs). The efficacy of inactivation was tested and compared for a wide spectrum of pathogens in PC and plasma, a subset of which is shown in **Tables 1 and 2**.

SUMMARY/CONCLUSIONS: Equivalent levels of inactivation (LRF difference ± 0.5 log) could be achieved for all pathogens in PC and plasma at the UVA light doses tested for INT200, except for *Klebsiella pneumoniae* in plasma and *Pseudomonas fluorescens* in platelets in 100% plasma, where a higher level of inactivation (difference in LRF > 0.5 log) was obtained using the INT200 Illuminator. Overall, these results demonstrate that the INT200 illuminator can provide similar performance compared to the INT100 for inactivating pathogens in donor PC and plasma.

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Table 1: Pathogen Inactivation in Platelets Using the INT100 and INT200 Illuminators

Pathogen	LRF (cfu/mL or pfu/mL) PC in 35% plasma/65% PAS-3		LRF (cfu/mL or pfu/mL) PC in 100% plasma	
	INT100 Illuminator	INT200 Illuminator	INT100 Illuminator	INT200 Illuminator
BTV	≥4.4	≥4.4	5.2	5.0
Ad5	>6.5	>6.5	≥5.7	≥5.4
DENV	>6.3	>6.3	>5.8	>5.8
BVDV	>4.7	>4.7	>4.6	>4.6
*Pseudomonas fluorescens**	≥7.8	≥7.6	6.6	7.5
*Klebsiella pneumoniae**	≥5.6	≥5.7	3.4	3.6
Clostridium perfringens	>6.6	>6.7	>6.7	>6.7
*Staphylococcus aureus**	>7.6	>7.6	≥7.7	≥7.7

* WHO approved bacterial reference strains provided by PEI were used

Table 2: Pathogen Inactivation in Plasma Using the INT100 and INT200 Illuminators

Pathogen	LRF (cfu/mL or pfu/mL)	
	INT100 Illuminator	INT200 Illuminator
BTV	≥4.3	≥4.3
Ad5	≥4.9	≥5.4
DENV	>6.0	>6.0
BVDV	>5.0	>5.0
*Pseudomonas fluorescens**	7.2	≥7.5
*Klebsiella pneumoniae**	4.5	5.1
Clostridium perfringens	>6.7	>6.7
*Staphylococcus aureus**	>6.5	>6.5

* WHO approved bacterial reference strains provided by PEI were used

Introduction of Amotosalen/UVA Pathogen-Reduced Pooled Plasma In a Swedish Blood Center: Impact on Production Efficiency, Clinical Availability and Cost

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BACKGROUND: Thawed fresh frozen plasma (FFP) is associated with high wastage rates due to unpredictable clinical demand. Pooled plasma may carry increased risk of transfusion-transmitted infection (TTI); however, treatment with the amotosalen/UVA (INTERCEPT®) pathogen reduction (PR) system can mitigate this risk. PR-plasma can also be thawed quickly when needed and stored at 2-6 °C for 5 days. In 2021-2023 a midsized blood center in Sweden converted from thawed single-donor whole blood (WB)-derived FFP stored up to 14 days to pooled PR-plasma units that are thawed on demand and proactively protect against TTI.

AIMS: To describe the impact of converting from thawed single-donor FFP to frozen-until-needed pooled PR-plasma on clinical availability, outdating rate, and plasma sales for fractionation.

METHODS: WB collections, FFP and PR-plasma production, outdating rates, per-patient use, and cost data were exported retrospectively from blood center records in Borås, a city of approximately 114,000 in western Sweden. Descriptive statistics were calculated for 2 periods: 2018-2020, only conventional FFP (P1) and 2021-2023, conversion to pooled PR-plasma (P2). PR-plasma was introduced in March 2021; the conversion to thawed-on-demand PR-plasma was finalized in October 2022. To produce PR-plasma, a pool of 5 thawed ABO identical FFP units (mean volume 260 mL) is pathogen reduced with the INTERCEPT® system before redistribution into 6 PR-plasma units of 200 mL and refrozen. The shelf life of thawed PR-plasma was reduced to 7 days (local variance).

RESULTS: A total of 5,183 WB-derived FFP units were produced during the 6-year study period. A total of 2,304 PR-plasma were produced in P2. A total of 1,970 were transfused in P1 (100%). In P2, 710 FFP (37.7%) and 1,175 PR-Plasma (62.3%) were transfused, respectively. PR-plasma transfusions increased from 13.6% in 2021 to 96.9% in 2023. The number of patients transfused with plasma increased 19% in P2 compared to P1 but the mean number of units per patient declined from 2.4 to 1.8. Thawing time decreased from ~17 minutes for FFP to ~7 minutes for PR-plasma. Despite shorter post-thaw shelf life of PR-plasma, outdating declined 48% in 2023 vs thawed FFP in 2018. The number of FFP units sold for fractionation increased 9% in 2023 vs 2018 while the rate of WB donations was approximately the same.

SUMMARY/CONCLUSIONS: Implementation of pooled PR-plasma stored frozen until needed required some additional labor (1 day/week of a technician's time) but contributed to reduced waste despite a shorter shelf life, improved production efficiencies, and increased revenue from plasma sales for fractionation. Efficiencies were attained through pooling of 5 WB-derived FFP units to produce 6 pooled PR-plasma units. Shorter thawing time of PR-plasma with standardized volume of 200 mL is of practical importance for emergency preparedness. The safety of PR-plasma is well documented in the literature; future studies may investigate the clinical advantages of less heterogenous pooled plasma, e.g., reduced transfusion reactions.

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	P1 (2018-2020) Mean (range)	P2 (2021-2023) Mean (range)	Total (2018-2023)	Change 2018 vs 2023
WB collections	8,892 (8,680-9,041)	8,853 (8,363-9,175)	53,235	+0.7%
FFP units produced	921 (770-1,060)	807 (752-893)	5,183	-26.8%
PR-Plasma units produced	-	2,304 (282-1,074)	2,304	-
FFP / PR-Plasma units transfused	657 (604-741)	628 (593-675)	3,855	-16.7%
FFP / PR-Plasma units outdated	233 (201-253)	147 (109-183)	1,140	-48.0%
FFP units sold for fractionation	7,401 (6,946-7,923)	7,552 (6,978-8,042)	44,859	+9.0%

Stability of Apheresis Plasma Treated With Amotosalen and UVA Stored for 3 Years

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BACKGROUND: In France, the shelf-life of plasma treated with amotosalen and UVA (FFP-A-UVA) for pathogen reduction (INTERCEPT™ Blood System, Cerus) is currently of 12 months from the date of collection.

AIMS: In the context of a need to extend the storage time for COVID-19 convalescent specific plasma, the stability of FFPA- UVA over 36 months was evaluated.

METHODS: 34 FFP-A-UVA triplets (3 units of at least 200 mL from the same COVID-19 convalescent apheresis plasma donation of up to 650 mL before A-UVA treatment) were selected from the frozen plasmas already stored (≤-25°C) at the EFS (Etablissement Français du Sang). 13 triplets were of group O and 21 of groups non-O. Fast freezing had been carried out after A-UVA treatment within 18 hours of collection. 30 plasma parameters as well as the Anti-SARS Cov-2 ELISA ratio were tested after 1 year (baseline, T1), 2 years (T2) and 3 years (T3).

RESULTS: **Table 1** presents the data for a selection of plasma parameters after 1 and 3 years of storage at ≤-25°C. The National requirements stipulating that at least 70% of the units should have a FVIII:C concentration ≥0.5 IU/mL and a fibrinogen concentration ≥2.0 g/L were met at both periods, (FVIII:C 94% at T1 and 97% at T3, Fibrinogen 82% at T1 and 88% at T3). All other plasma factors were within physiological ranges. The ratio of anti-SARS-Cov-2 antibodies showed a moderate decrease.

SUMMARY/CONCLUSIONS: The study on the *in-vitro* quality data of 34 units (triplets) of PFC-IA kept frozen at a temperature ≤ -25°C for up to 3 years shows a stability of this plasma with regards of tested parameters. Compliance with the applicable French regulatory requirements as defined by law was confirmed at all periods (T1, T2 (not shown) and T3). The possibility to store plasma for an extended time is of interest in the context of convalescent plasma program.

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Table 1: Results of a Selection of Parameters Tested at 1 and 3 Years of ≤-25°C Storage in FFP-A-UVA

Parameters Tested N=34 Average ± Standard Deviation	FFP-A-UVA -1 year: T1	FFP-A-UVA -3 years: T3	% RecoverySignificant (S) or non-significant (NS) difference* : T3/T1
PT (%)	95 ± 9	88 ± 9	93 ± 3 / S
APTT (ratio)	0.97 ± 0.09	0.97 ± 0.09	100 ± 3 / NS
Thrombin generation ETP (%)	93.43 ± 30.56	93.59 ± 29.50	101 ± 9 / NS
Fibrinogen (g/L)	2.45 ± 0.44	2.64 ± 0.46	108 ± 4 / S
Factor II (IU/mL)	0.85 ± 0.11	0.83 ± 0.10	98 ± 6 / S
Factor V (IU/mL)	0.88 ± 0.16	0.87 ± 0.15	99 ± 6 / NS
Factor VII (IU/mL)	0.91 ± 0.24	0.83 ± 0.20	91 ± 4 / S
Factor VIII:C (IU/mL)	0.72 ± 0.23	0.76 ± 0.20	107 ± 9 / S
Factor IX (IU/mL)	0.83 ± 0.16	0.81 ± 0.15	98 ± 6 / S
Factor X (IU/mL)	0.88 ± 0.17	0.85 ± 0.16	97 ± 7 / S
Factor XI (IU/mL)	0.85 ± 0.16	0.83 ± 0.16	98 ± 6 / S
Von Willebrand Factor VWF :RCo (%)	74 ± 27	76 ± 25	103 ± 7 / NS
Protein S (% activity)	76 ± 15	70 ± 15	92 ± 5 / S
TAT (µg/L)	2.2 ± 0.3	2.5 ± 0.4	117 ± 15 / S
C3a (µg/L)	92.82 ± 48.66	102.32 ± 40.25	122 ± 33 / NS
C5a (µg/L)	14.34 ± 5.43	11.85 ± 4.31	83 ± 8 / S
Anti-SARS CoV-2 ELISA ratio	6.43 ± 2.82	5.47 ± 2.95	85 ± 24 / S

* Student's t-test for paired samples. Significant difference if $p<0.05$.

Amotosalen/UVA Light Pathogen Reduced Pooled Plasma Stored Frozen for 3 Years and Liquid for 5 Days

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BACKGROUND: Two types of therapeutic plasmas are produced by the French Blood Service (EFS), plasma secured by quarantine (Q) and plasma pathogen reduced (PR) by amotosalen/UVA light treatment (A-UVA) (INTERCEPT™ Blood System, Cerus). A "previously frozen plasma" (PFP) process consisting after a frozen Q period in thawing the plasma, AUVA treating and refreezing for storage was validated. This PFP process is approved in France since November 2022.

AIMS: To evaluate 3-years frozen (≤-25°C) stability of A-UVA PFP with subsequent 5-days liquid (4°C) storage.

METHODS: 18 groups of 5 CPD whole blood derived plasma units were frozen and stored at <-25°C for 30 weeks. After thawing, pools of 5 units were constituted, split in 2x 640 mL minimum. Each of the two sub-pools was A-UVA treated, split in 3 units and frozen within 6 hours. All plasma units were non-O. Plasma parameters were measured in the thawed plasma pools after the Q period (baseline) and in the plasma units after A-UVA treatment and up to 14-days frozen storage (post treatment), and at 1, 2 and 3 years from collection. After 3 years of frozen storage the plasma units were thawed and stored at 4°C for 5 days. 30 plasma parameters were tested for the frozen storage study and 6 parameters for the liquid storage study.

RESULTS: The results of the 6 parameters tested in the 18 replicates through frozen and liquid storage are reported in the **Table** below. The requirements from the French Official Journal (JO), at least 70 % of the units with FVIII ≥0.5 IU m/L and Fibrinogen ≥ 2.0 g/L were met at all periods.

SUMMARY/CONCLUSIONS: Previously frozen plasma treated post-thawing with A-UVA retained sufficient levels of plasma proteins, coagulation factors and inhibitors and normal thrombin generation capacity. A sufficient stability of these parameters was observed over a 3-year storage period at ≤-25°C followed by 5-day storage at 4°C.

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N=18	Baseline (after 30-week ≤-25°C storage)	After thawing / A-UVA PR / & frozen storage up to 1-year from collection*	3 years from collection*	5 days post-thaw (4°C storage)**
Total proteins (g/L)	58,2 ± 2,0	60,1 ± 2,7 s	58,99 ± 2,19	59,28 ± 2,48
Fibrinogen (g/L)	2.65 ± 0.17	2.37 ± 0.14 s	2,50 ± 0,15 s	2,48± 0,17
FVIII (IU/mL)	1.10 ± 0.11	0.78 ± 0.09 s	00,74 ± 0,06 s	0,54±0.05 s
FVII (IU/mL)	1.03 ± 0.11	0.79 ± 0.08 s	00,8 ± 0,10 s	0.72±0.24
Prothrombin Fragment 1+2 (pM/L)	152.8 ± 28.4	147.8 ± 29.9	306,63 ± 107,32 s	360.60 ± 255.07
C3a (ng/ml)	245.8 ± 77.5	117.9 ± 44.0	169,23 ± 84,75 s	372 ± 146,42 s
Thrombin generation ETP – (nM thrombin x min) – Tissue factor 5 pM	1673.7 + 159.3	1477,9 + 202,1 s	1395,7 ± 117,8 s	1364,62 ± 127,48
Thrombin generation ETP – (nM thrombin x min) – Tissue factor 1 pM	1281,8 ± 219,6	1168,6 ± 198,7	1209,4 ± 162,0	1092,34 ± 251,41 s

* two-tailed (alpha 0.05) t-test for paired values comparing each frozen storage period to the "pre" data, "s" if significant difference $p < 0.05$.

** two-tailed (alpha 0.05) t-test for paired values comparing 5-day post thaw to 3-year frozen storage data, "s" if significant difference $p < 0.05$.

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N=18	Baseline (after 30-week ≤-25°C storage)	After thawing / A-UVA PR / & frozen storage up to 1-year from collection*	2 years from collection*	3 years from collection*	5 days post-thaw (4°C storage)**
Total proteins (g/L)	58,2 ± 2,0	60,1 ± 2,7 s	60,4 ± 2,1 s	58,99 ± 2,19	59,28 ± 2,48
Fibrinogen (g/L)	2.65 ± 0.17	2.37 ± 0.14 s	2,43 ± 0,16 s	2,50 ± 0,15 s	2,48± 0,17
FVIII (IU/mL)	1.10 ± 0.11	0.78 ± 0.09 s	0,72 ± 0,08 s	00,74 ± 0,06 s	0,54±0.05 s
FVII (IU/mL)	1.03 ± 0.11	0.79 ± 0.08 s	0,81 ± 0,08 s	00,8 ± 0,10 s	0.72±0.24
Prothrombin Fragment 1+2 (pM/L)	152.8 ± 28.4	147.8 ± 29.9	140,6 ± 25,3 s	306,63 ± 107,32 s	360.60 ± 255.07
C3a (ng/ml)	245.8 ± 77.5	117.9 ± 44.0	209,3 ± 125,2	169,23 ± 84,75 s	372 ± 146,42 s
Thrombin generation ETP – (nM thrombin x min) – Tissue factor 5 pM	1673.7 + 159.3	1477,9 + 202,1 s	1265,7 ± 151,0	1395,7 ± 117,8 s	1364,62 ± 127,48
Thrombin generation ETP – (nM thrombin x min) – Tissue factor 1 pM	1281,8 ± 219,6	1168,6 ± 198,7	981,5 ± 227,8	1209,4 ± 162,0	1092,34 ± 251,41 s

Implementation of Pathogen-Reduced Cryoprecipitated Antihemophilic Factor from Restricted Quarantine Plasma to Maintain Adequate Supply

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BACKGROUND: Massive bleeding protocols require the transfusion of cryoprecipitated antihemophilic factor (CP) as the main source of fibrinogen in our institution. It was manufactured from released quarantine fresh frozen plasma (QFFP), to ensure product safety. The demand for CP increased 64%, from 2019 (1082 units) to 2020 (1779 units) and another 216%, from 2020 to 2021 (5615 units). The increased demand was mainly driven by the COVID-19 pandemic (ECMO treatment of severe COVID-19). From 2020, the available released QFFP quantities were not sufficient to meet the demand of CP in our institution. To overcome that shortage, we evaluated the production of CP from pathogen-reduced (PR) restricted (non-released) QFFP and introduced PR-CP in Q3/2021. In 2023, the demand for CP was still on a comparable high level, mainly due to the opening of a new emergency ICU, leading to permanent production of PR-CP. For long-term implementation, we developed a new production method for improved PR-CP quality.

AIMS: Evaluation of the quality treatment-eligibility of PR-CP from restricted QFFP and optimization of the production process.

METHODS: 650 mL of FFP was collected by apheresis with an Aurora device (Fresenius Kabi, Germany) or a PCS2 device (Haemonetics, U.S.A.). 430 mL were treated with amotosalen/UVA technology (INTERCEPT Blood System, Cerus, U.S.A.), treated- and untreated plasma units were subsequently frozen within 6 h post collection at -40°C. CP was produced by thawing at 4°C for 18 h followed by centrifugation at 4°C with an RC 3C+ centrifuge (Sorvall, U.S.A.). The final target volume of a single CP unit from approx. 210-220 mL plasma is 40 mL. The fibrinogen content and plasma factors quantity were determined with an ACL TOP 750 device (Werfen, Germany). CP thawing was conducted with either a water bath or a Sahara-III plasma thawer (Sarstedt, Germany). Statistical analysis was conducted with the student t-test.

RESULTS: Patients in the infectious diseases ward received on average 10.3 CP transfusions/patient, while other patients in the emergency unit received in average 6.6 CP units/patient ($p<0.001$) in 2021. The average fibrinogen content of a conventional CP unit from 220 mL QFFP was 0.23 g and of a PR-CP-Unit 0.19 g ($p<0.05$). Increasing the QFFP volume pre-PR-treatment from 220 mL to 325 mL resulted in an average fibrinogen content of 0.23 g, comparable to a conventional CP unit. In a comparative analysis, the fibrinogen content was 57.1% higher when we used a plasma thawer (average 0.22 g) compared to a water bath (0.14 g/L) (n=25, $P<0.001$) for thawing CP. In Q4/2021 11% of the issued CP was PR-CP, 40% from plasma outside our center. In Q1/2022 62% of the issued CP was PR-CP, only 1% from plasma outside our center. A modified production method (M2) including plasma pooling pre-PR-CP production was compared to our standard method of pooling PI-CP post-production (M1). Twelve 240 mL CP units were produced with each method from 24 PR-QFFP units. The fibrinogen content was 1.1 (0.8-1.6) g/dose in M1 PI-CP and 1.5 (0.9-2.1) in M2 PI-CP ($p<0.05$). The FVIII content was 362 (249-524) IU/dose in M1 PI-CP and 415 (287-721) in M2 PI-CP ($p>0.05$). The average FXIII content was 274 (201-358) IU/dose in M1 PI-CP and 359 (280-358) in M2 PI-CP ($p<0.05$).

SUMMARY/CONCLUSIONS: The introduction of PR-QFFP allowed us to fulfill the growing CP demand and to maintain selfsufficiency. Improved production methodology increased the average content of fibrinogen (36%) and FXIII (31%) significantly.

The Impact of Plasma Pooling, Pathogen-Reduction and the Freeze/Thaw Process On Plasma Quality and Standardization

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BACKGROUND: In Poland, plasma must be quarantined or pathogen-reduced to increase blood safety, especially with respect to potential window-period infections. The majority of plasma is derived from whole blood donations, with a high variability in the total protein profile and volume, due to individual donor factors and production methodology. Plasma pooling to obtain a more standardized product was not common due to potential pathogen transmission risk increase. We implemented a 5 single-donor plasma (SDP) units plasma pooling concept in combination with pathogen-inactivation to generate 6 pathogen-reduced, pooled plasma (PPP) therapeutic units. Besides product standardization and blood safety this has an economic impact, allowing for the production of 20% more plasma units from whole blood donations.

AIMS: Assessment of the impact of plasma pooling, PI-treatment and the plasma freeze/thaw process on plasma product quality and standardization.

METHODS: Plasma was produced from whole blood (WB) donations with the buffy coat method using a Compomat G5 automated press (Fresenius-Kabi, Germany). Five ABO-identical SDPs were pooled using an Optipool DONOpack plasma pooling set (LMB Technologies, Germany) (1250-1300 mL). After mixing, the pool was separated into 2 minipools (625-650 mL), which subsequently were pathogen-reduced with the amotosalen/UVA technology (INTERCEPT Blood System for Plasma, Cerus). In the integrated disposable set, the minipools were separated into 3 storage bags, resulting in 6 PPPs. The plasma units were frozen within 8 hours after preparation using a plasma freezer (MABAG, Germany) and stored at -30°C. Analysis for FVIII (chronometric assay), fibrinogen (Clauss method) and total protein content (colorimetric assay) was conducted using a bk6100 analyzer (bio-ksel, Poland) in a standardized procedure.

RESULTS: Five experiments pooling 5 SDPs were conducted. The average volume of SDPs (n=25) was 267.4±4.7 mL, (range 21.4±10.1 mL). The average volume of PPPs (n=30) was 219.4±2.4 mL range (0.6±0.5 mL, a variability reduction of 97.2%). The average total volume loss during processing was 1.7±1.0%. The average fibrinogen content of SDPs was 324.6±30.0 mg/dl, (range 114.0±88.0 mg/dl). The average fibrinogen content of PPPs was 264.1±24.0 mg/dl, with a recovery of 81.3%. Post freezing for 1 month the recovery was 232.2±24.3 (71.5%). The average range was 18.6±1.8 mg/dl (a variability reduction of 81.1%). The average FVIII content of SDPs was 131.0±16.4 IU/dl, (79.1±43.9 IU/dl). The average FVIII content of PPPs was 96.4±17.1 IU/dl, a recovery of 73.4%. Post freezing for 1 month the recovery was 85.5±16.9, (65%). The average range was 26.6±7.4 IU/dl (a variability reduction of 66.4%). The average total protein content of SDPs was 60.7±2.7 g/L, the range 8.3±2.4 g/L. The average total protein content of PPPs was 57.5±2.3 g/L, a recovery of 94.7%. After freezing for 1 month the recovery was 56.5±1.4, a recovery of 92.9%. The average range was 1.0±0.6 g/L (a variability reduction of 87.9%).

SUMMARY/CONCLUSIONS: The product quality post-treatment was within EDQM (FVIII ≥50 IU/dl, ≥60% fibrinogen recovery) and Polish guidelines (FVIII ≥50 IU/dl, FVIII recovery ≥70%, total protein ≥50 g/L, fibrinogen recovery ≥60%). The volume variability between plasma units (range between highest and lowest values) was reduced in average for 97.2% comparing PPPs to SDPs, the plasma factor/proteins variability in average for 78.5%, increasing product standardization.

Evaluation of Plasma Treated for Pathogen Reduction With Amotosalen and a Prototype LED Illuminator

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BACKGROUND: The INT100 illuminator used for INTERCEPT™ Blood System (Cerus) processing of platelets and plasma provides a controlled amount of ultraviolet A (UVA) light emitted by fluorescent bulbs. Cerus has developed a new illuminator with a light-emitting diode (LED) light source that is currently being validated. The ergonomics, the software and the user interface have been updated.

AIMS: The purpose of this study is to evaluate the quality of fresh frozen whole blood-derived pooled plasma pathogen reduced by amotosalen and UVA LED light (FPP A-UVA), using a pre-production LED illuminator.

METHODS: 19 pools of 5 units of plasma derived from leukocyte depleted whole blood were prepared, then divided into 2 parts of close to 650 mL, each connected to an INT31 plasma processing set and treated with amotosalen and UVA (LED light), before excess compound adsorption (through a CAD) and freezing to ≤-25°C within 9 ± 1 hours. The results of a selection of parameters out of the 30 tested before treatment (T2), then after treatment & CAD before freezing (T3), and after 3 months (T4: not shown), and 1 year (T5) at ≤-25°C, are presented.

RESULTS: The results of the analyses are shown in **Table 1**. FFP A-UVA treated with the LED illuminator complies with the French regulatory requirements (Official Journal of 4 June 2020) of at least 70 % of the units with Factor VIII:C ≥ 0.50 IU/mL and Fibrinogen concentration ≥2.0 g/L, with 100% compliance after 1-year storage, and are equivalent to those obtained in routine quality control with INT100. All tested parameters at T5 are within ±25% of T2 baseline values, except Factor VIII (69.2%), TAT (62.3%) and C3a (16.2%, effect of the CAD).

SUMMARY/CONCLUSIONS: The process of preparing pathogen reduced plasma with amotosalen and UVA generated by a LED illuminator delivers products that meet the expectations with regard to the quality of therapeutic plasma after frozen storage of at least one year. The LED illuminator brings advances in ergonomics and user interface.

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Table 1: Results of a Selection of Parameters Tested at Different Time Periods in FFP A-UVA Treated with a LED Illuminator

N=19	T2 Pre-treatment pool	T3 FFP A-UVA after CAD	T5* FFP A-UVA 1 year at ≤-25°C	T5/T2
Total Proteins (g/L)	60.08 ± 1.45	57.79 ± 1.45	59.21 ± 1.18 s	98.5%
PT (%)	107 ± 7.0	98 ± 6.8	91 ± 4.4 s	85.0%
APTT (ratio)	0.85 ± 0.05	0.88 ± 0.04	0.99 ± 0.05 s	117.0%
Endogenous thrombin potential (ETP) (%)	112,9 ± 8,5	112,1 ± 8,6	102.7 ± 12.1 s	90.9%
Fibrinogen (g/L)	2.68 ± 0.16	2.43 ± 0.17	2.49 ± 0.16	93.1%
Factor II (IU/mL)	1.06 ± 0.07	0.92 ± 0.07	0.80 ± 0.06 s	76.1%
Factor V (IU/mL)	0.88 ± 0.07	0.86 ± 0.07	0.82 ± 0.06 s	92.9%
Facteur VII (IU/mL)	0.99 ± 0.13	0.86 ± 0.09	0.81 ± 0.09	81.2%
Factor VIII (IU/mL)	1.15 ± 0.25	0.83 ± 0.18	0.79 ± 0.17	69.2%

*Paired t-test T5 versus T3 – « s » if significant difference $p<0.05$

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Table 1 Continued: Results of a Selection of Parameters Tested at Different Time Periods in FFP A-UVA Treated with a LED Illuminator

N=19	T2 Pre-treatment pool	T3 FFP A-UVA after CAD	T5* FFP A-UVA 1 year at ≤-25°C	T5/T2
Factor IX (IU/mL)	0.98 ± 0.09	0.80 ± 0.07	0.77 ± 0.06	78,2%
Willebrand activity(Rco %)	85 ± 16.5	82 ± 16.5	90 ± 17.8	105.8%
Protein S (% activity)	100 ± 8.4	91 ± 7.0	85 ± 8.3 s	85.9%
Antithrombin (% activity)	102 ± 5.1	96 ± 4.2	97 ± 4.4	94.8%
alpha 2-antiplasmin (% activity)	102 ± 3.4	87 ± 4.0	79 ± 3.6 s	77.2%
Plasminogen (%activity)	95 ± 5.2	87 ± 5.1	85 ± 5.3	89.5%
TAT complexes (µg/L)	43 ± 24.7	39 ± 22.2	27 ± 15.3	62.3%
ADAMTS 13 (%activity)	101 ± 16.8	94 ± 11.2	84 ± 6.5 s	82.8%
C3a (µg/l)	384,6 ± 105,5	10.4 ± 5.2	62.3 ± 18.7 s	16.2%

*Paired t-test T5 versus T3 – « s » if significant difference $p<0.05$

Amotosalen-UVA Pathogen Reduced Plasma, Cryoprecipitate Reduced (PRPCR): An Optimized Cost-Effective Component for Therapeutic Plasma Exchange

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BACKGROUND: Cryoprecipitate poor plasma (CPP) is underutilized for therapeutic plasma exchange (TPE). Mafra (American Society of Hematology Abstract # 2629, 2024) reported a meta-analysis of TPE for thrombotic thrombocytopenic purpura (TTP) showing decreased mortality with CPP compared to plasma. Solvent detergent plasma (SDP) is used for TTP and albumin for other TPE to reduce risk of transfusion-transmitted infection (TTI). FDA approved amotosalen-UVA Pathogen Reduced Plasma, Cryoprecipitate Reduced (PRPCR: Cerus, Concord, CA) for TPE of TTP and other indications to reduce risk of TTI.

AIMS: To characterize the hemostatic functions of PRPCR.

METHODS: Thrombin Generation (expressed as endogenous thrombin potential- ETP), Fibrinogen (FIB), Factors II, V, VII, VIII, IX, X, XI were measured by one-stage coagulation assays. VWF was measured by Ristocetin platelet aggregation (RIPA). ADAMTS13 was measured by FRETS assay. Protein C, Protein S, and α-2 plasmin inhibitor (α-2 PI) were measured by standardized assays. IgG and IgA were assessed by nephelometry and SDS PAGE. The ability of FIB and vWF from PRPCR to support platelet adhesion and aggregation were determined in microfluidic chambers at various wall shear rates. For these experiments, we used hirudinated whole blood or reconstituted plasma-free blood (RBC + platelets + PRPCR or PR cryoprecipitated fibrinogen complex, IFC).

RESULTS: (**Tables 1-2**). In PRPCR: FIB, Factor VIII, and vWF were reduced compared to plasma. Factors II, V, VII, IX, X, XI, Protein C, Protein S, and α-2 PI were conserved. IgG levels were retained without qualitative changes. Thrombin generation was reduced with retained activity (**Table 1**). Microfluidic assays at low shear (300 s^{-1}) confirmed PRPCR (FIB = 50 mg/dL) surface coating promoted platelet adhesion, which was reduced compared to IFC (FIB = 300 mg/dL). Integrin αII-bβ3 played a key role in adhesion with complete inhibition by abciximab for both conditions, indicating the GPIb-IX-V complex is only partly involved. Perfusion of reconstituted blood over immobilized vWF binding peptide (100 μg/mL), showed absence of platelet adhesion with PRPCR compared to IFC full activity. Perfusion of reconstituted blood over immobilized collagen (200 μg/mL) at high wall shear rate (3,000 s^{-1}) resulted in no platelet aggregation with PRPCR compared to IFC.

SUMMARY/CONCLUSIONS: PRPCR retained thrombin generation, anti-thrombotic proteins, and ADAMTS13. Residual fibrinogen supported platelet adhesion at low shear. Collagen induced platelet aggregation was negligible at high shear due to depletion of high molecular weight vWF. PRPCR retains functional hemostatic capacity for TPE without increased platelet thrombotic activity while providing retention of IgG and IgA, and the benefit of pathogen reduction.

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Table 1	PRPCR	PR Plasma
Thrombin Generation-ETP (nM . min)	1156 ± 208	1581 ±154
Fibrinogen (mg/dL)	1.47 ± 0.15	2.28 ± 0.49
Factor II (IU/mL)	0.77 ± 0.07	0.89 ± 0.12
Factor V (IU/mL)	0.66 ± 0.12	0.86 ± 0.17
Factor VII (IU/mL)	0.83 ± 0.21	0.77 ± 0.23
Factor VIII (IU/mL)	0.15 ± 0.05	0.92 ± 0.35
Factor IX (IU/mL)	1.00 ± 0.19	1.00 ± 0.25
Factor X (IU/mL)	0.86 ± 0.13	0.94 ± 0.19
Factor XI (IU/mL)	1.02 ± 0.29	0.92 ± 0.21

Table 2	PRPCR	PR Plasma
vWF RIPA (IU/mL)	0.10 ± 0.00	0.95 ± 0.38
ADAMTS 13 (IU/mL)	1.32 ± 1.8	0.90 ± 1.6
Protein C (IU/mL)	0.99 ± 0.14	0.79 ± 0.18
Protein S (IU/mL)	0.83 ± 0.10	0.97 ± 0.23
α-2 plasmin inhibitor (IU/mL)	0.86 ± 0.13	0.76 ± 0.07
IgG (mg/g total protein)	989.9	993.5
IgA (mg/g total protein)	13.7	14.2

INTERCEPT REGULATORY APPROVALS

Canada (Health Canada)
2016 (plasma), 2018 (platelets)

Brazil (ANVISA)
2015 (platelets and plasma)

United States (FDA)
2014 (platelets and plasma)

Mexico (COFEPRIS)
2014 (platelets and plasma)

Singapore (HSA)
2014 (platelets)

Switzerland (Swissmedic)
2009 (platelets), 2010 (plasma)

Germany (PEI)
2007* (platelets), 2011* (plasma)

France (ANSM)
2003 (platelets), 2006 (plasma)

CE Mark, Class III
2002 (platelets), 2006 (plasma)

*** First blood center marketing authorization approved.**

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Consult instructions for use for indications, contraindications, warnings, and precautions.