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PROGRAM OF ABSTRACTS

# ISBT 2023

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**Poster-Session Date: Monday, June 19, 2023**

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# *In Vitro* Biochemical and Functional Comparison of Amotosalen-UVA-Treated Buffy-Coat Platelet Concentrates Stored in PAS-C Or PAS-E Additive Solution up to 7 Days

**B Hechler[1,2], N Brouard[1,2], F Rudwill[2], C Mouriaux[1,2], A Koll[2], D Haas[2], A Galvanin[2], D Kientz[2], P Mangin[1,2], H Isola[2]**

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**BACKGROUND**: Deterioration in the quality of platelet concentrates (PCs) during storage results from changes of various biochemical and metabolic parameters affecting platelet hemostatic properties and survival after transfusion. These lesions depend on the methods used for preparation and pathogen inactivation, the duration of storage and the type of platelet additive solutions (PAS) used. However, there exists no detailed comparison of PAS-C (InterSol/PAS-III, Fresenius) and PAS-E (SSP+, Macopharma), a modification of PAS-C containing 5 mM KCl and 1.5 mM MgCl2, for the conservation of buffy-coat (BC)-PCs treated with amotosalen-UVA (INTERCEPT Blood System, Cerus) with regard to the storage changes including *in vitro* platelet functional properties.

**AIMS**: We evaluated the *in vitro* quality of BC-PCs treated with INTERCEPT and stored up to 7 days in either PAS-C or PAS-E.

**METHODS**: A pool-and-split strategy was used to obtain two study groups (n=5 per group): i) double-dose BC-PCs collected into PAS-C/plasma (55/45) treated with amotosalen-UVA, ii) double-dose BC-PCs collected into PAS-E/plasma (55/45) treated with amotosalen-UVA. The *in vitro* quality and function of the platelet components were tested over 7 days of storage post collection at 22-24°C.

**RESULTS**: Platelet counts were conserved in both groups of PCs during storage, as was platelet swirling without the appearance of macroscopic aggregates. Storage in PAS-C resulted in a significant increase in mean platelet volume (MPV) as of day 3, as compared to storage in PAS-E, where it remained stable. Integrin $\alpha$IIb$\beta$3 and glycoprotein (GP) VI expression remained stable in both solutions, whereas GPIb$\alpha$ and GPV declined similarly in both groups. Storage in PASE resulted in a significant reduction in glucose consumption and lactate generation as compared to storage in PAS-C on day 5.5, with better maintenance of pH levels as of day 3. Notably, sufficient glucose was still available on day 7 in PCs stored in PAS-E compared to PCs stored in PAS-C. Spontaneous P-selectin exposure, a marker of $\alpha$-granule secretion, was significantly reduced in PCs stored in PAS-E as compared to PAS-C as of day 1.5. The proportion of activated $\alpha$IIb$\beta$3 remained globally low and similar in both study groups. Spontaneous phosphatidylserine (PS) exposure at the surface of platelets, a marker for platelet activation and apoptosis evaluated by annexin V binding, significantly increased during late storage of PCs in PAS-C compared to PCs conserved in PAS-E where it remained stable. Mitochondrial transmembrane potential, evaluated using the tetramethylrhodamine methyl ester (TMRM) fluorescent dye retained in functional intact mitochondria, diminished significantly in PCs stored in PAS-C but not in PAS-E as of day 5. Lactate dehydrogenase (LDH) release, an indication of premature platelet lysis, was significantly reduced in PCs stored in PAS-E as compared to PAS-C, as of day 5.5. During storage, both PAS-C and PAS-E platelets retained capacity to adhere to VWF and fibrinogen, and to form aggregates of similar thrombus volume on collagen in a microfluidic shear flow chamber.

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**SUMMARY/CONCLUSIONS**: Use of PAS-E/plasma improved platelet metabolism, reduced spontaneous activation, reduced apoptosis and reduced LDH release, as compared to PAS-C/plasma, especially during the late stages of storage, without differences in *in vitro* platelet adhesive properties. This study highlights the strong influence of the composition of the additive solution on the occurrence of storage lesions in pathogen-reduced PCs.

# Platelet Safety Measures in Sweden: An Assessment of Current Practices and Comparison with International Practices

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**BACKGROUND**: In Sweden, platelet components (PCs) are produced by 28 blood centers. Bacterial control measures for PCs (donor skin preparation, diversion pouches) are based on European (EDQM) guidelines. Safety measures including pathogen reduction (PR) or large volume delayed sampling (LVDS) bacterial culture are widely used but are not required by national guidelines, except to extend shelf-life from 5 to 7 days.

**AIMS**: Document PC safety measures in Sweden and assess LVDS methods used in Sweden against international LVDS practices.

**METHODS**: All Swedish blood centers were invited to submit data from 2020 on PC production and bacterial safety measures via an electronic survey tool. Data were stratified by location, bacterial safety measure used (PR, LVDS, none), and PC shelf-life (5 or 7 days). Bacterial culture practices were stratified by sample volume, sampling delay and use of aerobic/anaerobic bottles. Consensus methods for LVDS were based on practices in the United Kingdom (UK), United States (US) and Canada. Comparative transfusion-transmitted bacterial infection (TTBI) risk data were compiled from the literature.

**RESULTS**: Complete data for 2020 were received from all 28 Swedish blood centers. A Total of 52,497 PCs were produced of which nearly 72% were pooled PCs prepared either from buffy coats or interim platelet units (IPU) separated by Reveos®. Fourteen centers (50%) producing >24,000 PR PCs with 7-day storage (46% of national PC supply) had adopted PR with the amotosalen/UVA technology (INTERCEPT™ Blood System). Eleven centers (39%) used LVDS to extend PC shelf-life to 7 days. Three centers (11%) produced 5-day PCs with no supplemental safety measure. LVDS was performed for 12,747 PCs (45% of non-PR PCs). In 2020, 5 bacterial contaminations were detected with LVDS (1/2,549 PCs screened). No TTBIs were reported to a voluntary hemovigilance system. Sampling volumes and timeframes differed widely among the 11 LVDS sites (**Table 1**). None of LVDS methods reported in Sweden matched consensus practices for sampling delay, volume and use of aerobic and anaerobic culture in the US, UK and Canada (**Table 2**). Hemovigilance data from countries that have converted from bacterial culture to PR or from standard culture to LVDS show the persistence of TTBI risk when culture is performed with smaller samples and earlier sampling.

**SUMMARY/CONCLUSIONS**: Nearly half of PCs produced in Sweden are treated with a PR technology to protect against a broad spectrum of bacteria. However, most PCs are produced using sub-optimal LVDS methods compared to other industrialized countries. Increased TTBI risk has been associated with bacterial culture methods using smaller samples and shorter sampling delays.

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**Table 1: Swedish LVDS Practices in 2020 (n=11)**

| Swedish blood centers using LVDS * | Sampling delay (hrs) | Sampling volume (mL) | Aerobic | Anaerobic (facultative) |
|---|---|---|---|---|
| A, B, C | ≥24-<48[a] | 10 | √ | - |
| D | <24 or ≥24-<48[b] | 8 | √ | - |
| E | <24[c] | 8 | √ | - |
| F, G | ≥24-<48[d] | 8 | √ | √ |
| H | <24 or ≥24-<48[e] | 4 | √ | - |
| I | ≥24-<48 | 4 | √ | - |
| J | ≥24-<48 | 4 | √ | √ |
| K | ≥48 | 4 | √ | √ |

*) Blinded for confidentiality; results reflect the majority of PCs screened. Exceptions described below.

a) Friday apheresis: <24 or ≥48 hrs b) ~50% in each category

c) Occasionally ≥24-<48 hrs d) Saturday apheresis: ≥48 hrs

e) Apheresis PCs: <24 hrs. Pooled PCs: ≥24-<48 hrs

**Table 2: International LVDS Consensus Practices**

| Country | Sampling delay (hrs) | Sampling volume (mL) | Aerobic (mL) | Anaerobic (mL) |
|---|---|---|---|---|
| United Kingdom (NHSBT) | ≥36 | 16 | 8 | 8 |
| Canada (Canadian Blood Services) | ≥36 | 20[a] | 8-10 | 8-10 |
| Canada (Héma-Québec) | ≥48 | 20 | 10 | 10 |
| United States (FDA)[b] | ≥48 | 16 | 8 | 8 |

a) For double apheresis PC, 40 mL volume, with 3 aerobic and 1 anaerobic bottle.

b) Apheresis PCs only. Each split apheresis PC should be sampled separately.

# *In Vitro* Biochemical and Functional Characteristics of Stored (Double-Dose) Buffy-Coat Platelet Concentrates Treated With Amotosalen and a Prototype UVA Light-Emitting Diode Illuminator

**B Hechler[1,2], N Brouard[1,2], F Rudwill[2], C Mouriaux[1], 2, A Koll[2,2], D Haas[2], A Galvanin[2], D Kientz[2], P Mangin[1,2], H Isola[2]**

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**BACKGROUND**: Pathogen reduction of platelet concentrates (PCs) using amotosalen and broad-spectrum UVA illumination contributes to the safety of platelet transfusion by reducing the risk of transfusion-transmitted infections.

**AIMS**: We evaluated the *in vitro* quality of stored buffy-coat (BC) PCs treated with amotosalen and a prototype narrow band width light emitting diode (LED) illuminator.

**METHODS**: A pool-and-split strategy was used to obtain four study groups (n=5 per group): i) double-dose BC-PCs prepared with PAS-C (InterSol)/plasma (55%/45%) treated with amotosalen and a conventional UVA lamp (INT100 illuminator 320-400 nm wavelengths, 3.9 J/cm$^2$), ii) double-dose BC-PCs prepared in PAS-C/plasma (55%/45%) and treated with amotosalen and a LED lamp (350 nm, 3.3 J/cm$^2$), iii) double-dose BC-PCs prepared in PAS-E (SSP+)/plasma (55%/45%) and treated with amotosalen and a conventional UVA lamp, iv) double-dose BC-PCs prepared in PASE/plasma (55%/45%) and treated with amotosalen and a LED lamp. The *in vitro* quality and function of the platelets were evaluated by multiple biochemical and functional assays over 7 days of storage.

**RESULTS**: Platelet counts were conserved during storage in all groups of PCs, as was platelet swirling without the appearance of macroscopic aggregates. Integrin $\alpha$IIb$\beta$3 and glycoprotein (GP) VI expression remained stable, whereas GPIb$\alpha$ and GPV declined similarly in all groups. UVA lamp- and LED-treated PCs displayed similar glucose consumption, lactate generation and pH levels. They also displayed comparable spontaneous P-selectin, phosphatidylserine and activated $\alpha$IIb$\beta$3 exposure, and similar maximal activation of these parameters upon strong agonist challenge, irrespective of the type of illuminator. Mitochondrial membrane potential, an indicator of mitochondria integrity, and lactate dehydrogenase (LDH) release, to evaluate premature platelet lysis, were similar for UVA lamp- and LED-treated PCs during storage. Finally, platelets prepared with both light sources and storage solutions retained adhesion to VWF and fibrinogen, and aggregate formation with similar thrombus volume on collagen under shear stress flow conditions over 7 day storage.

**SUMMARY/CONCLUSIONS**: Replacing fluorescent UVA lamps with LED lamps for INTERCEPT treatment had no impact on platelet metabolism, spontaneous activation, apoptosis or viability, or on the *in vitro* hemostatic function of BC-PCs stored for 7 days in PAS-C or PAS-E/plasma.

# Evaluation of the *In Vitro* Properties Out to 7 Days of Buffy Coat Platelets Stored In PAS C Or PAS E and Treated With Amotosalen and a Prototype LED UVA Light Source

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**BACKGROUND**: Pathogen inactivation of platelets is implemented as a standard of care by EFS. The technique (INTERCEPT® Blood System, Cerus) combines amotosalen and a UVA light source (A-UVA). The UVA dose is delivered by an Illuminator equipped with fluorescent bulbs. Light emitting diodes (LED) in the target UVA wavelength are becoming available as alternate light sources. EFS has adopted a double dose platelet production method for whole blood derived platelet concentrates using pools of 8 buffy coats (BC-PCs). Pools are prepared in PAS C or PAS E platelet additive solution.

**AIMS**: To evaluate the *in vitro* properties out to 7 days of BC-PCs stored in PAS C or PAS E and treated with A-UVA using a prototype LED Illuminator.

**METHODS**: 16 BC-PCs were prepared from pools of 8 BCs with TACSI+ (Terumo BCT) separators in 32-47% plasma and 53-68% PAS using 300 ml of either PAS C (InterSol, Fresenius Kabi) or PAS E (SSP+, Macopharma). The BC-PCs were treated with double dose processing sets (DS) using 17.5 ml of 3 mM amotosalen and UVA light (3.3 J/cm$^2$) delivered by a prototype LED Illuminator (Cerus) followed by 6-16 hours storage in a compound adsorption device (CAD). BC-PCs were stored for 7 days and sampled at day (D) 1 (pre), D2 (post PI), D5, and D7 for the evaluation of platelet characteristics and quality markers: platelet content, pH, glucose, lactate, Mean platelet volume, $pO_2$, $pCO_2$, LDH, soluble p-selectin.

**RESULTS**: Table 1 summarizes the characteristics of BC-PC's after the A-UVA and CAD processing steps and split into two final storage containers. All units met the French guidelines for these characteristics.

**SUMMARY/CONCLUSIONS**: The change of UV-A source to prototype LED had no substantial effect on 7- day storage properties of A-UVA BC-PCs. The use of PAS E in comparison with PAS C slightly improved platelet metabolism and generated less spontaneous activation or signs of apoptosis.

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**Table 1: Characteristics of A-UVA BC-PCs in PAS C and PAS E (combined results at D2)**

| N=16 | Volume (mL)* | Platelet concentration ($10^9$/L)* | Platelet content ($10^{11}$)* |
|---|---|---|---|
| Mean ± standard deviation | 174 ± 6 | 1699 ± 194 | 3,0 ± 0,4 |
| French guidelines | ≥100 | ≥ 600 | ≥ 2,0 x $10^{11}$ |

*After split of the double dose BC-PCs in 2 final storage containers

**Table 2: Presents the Main *In-Vitro* Storage Properties of the A-UVA BC-PCs Over 7 Days**

| PAS C N=8 | Day 1 (pre-A-UVA) | Day 2 | Day 5 | Day 7 |
|---|---|---|---|---|
| pH (22°C) | 7.22 ± 0.11 | 7.10 ± 0.13 | 6.91 ± 0.05 | 6.90 ± 0.05 |
| Glucose (mmol/L) | 8.3 ± 0.4 | 7.5 ± 0.5 | 1.1 ± 0.7 | 0.0 |
| LDH (U/L) | 76 ± 7 | 94 ± 16 | 157 ± 17 | 211 ± 23 |
| p-selectin (ng/mL) | 31.2 ± 6.3 | 42.7 ± 10.3 | 116.0 ± 25.5 | 224.5 ± 35.1 |
| **PAS E N=8** | **Day 1 (pre-A-UVA)** | **Day 2** | **Day 5** | **Day 7** |
| pH (22°C) | 7.17 ± 0.03 | 7.06 ± 0.03 | 7.2 ± 0.06 | 7.07 ± 0.08 |
| Glucose (mmol/L) | 8.1 ± 0.6 | 7.3 ± 0.6 | 4.0 ± 0.7 | 1.4 ± 0.9 |
| LDH (U/L) | 93 ± 23 | 102 ± 9 | 137 ± 23 | 168 ± 29 |
| p-selectin (ng/mL) | 30.4 ± 12.2 | 36.1 ± 8.0 | 70.2 ± 9.9 | 129.3 ± 25.4 |

The *in vitro* biologic parameters reflect metabolism and an evolution of storage lesions comparable to the data (not shown) reported for previous A-UVA validations using a fluorescent UVA light source. All the units retained a relatively stable pH and retained swirling between D1 and D7. A significant difference was observed per an analysis of variance in favor of PAS E versus PAS C for the following parameters: pH, glucose, LDH, soluble p-selectin.

# Amotosalen and UVA Treatment of *Enterobacter soli*, *Leclercia adecarboxylata*, and *Staphylococcus saprophyticus* 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 apheresis- and whole-blood derived platelets. In 2021, a report of an infection involving an INTERCEPT treated apheresis PC at a clinic in the United States was published. Three bacteria were isolated from the bag and identified by sequencing as *Enterobacter soli*, *Leclercia adecarboxylata* and *Staphylococcus saprophyticus*. It could not be excluded that the PC was contaminated after the treatment as the bag was discarded before analysis of the unit could be performed. Prior TTIs associated with an INTERCEPT-treated PC have shown defects in the bag that lead to external contamination after treatment (Fadeyi *et al*., *Transfusion*, 2020). A previous study has also shown that *L. adecarboxylata* and *S. saprophyticus* can be inactivated by the INTERCEPT Blood System for Platelets (Fadeyi *et al*., *Transfusion*, 2020). This was the first report of an *E. soli* contaminated platelet unit and infection of a human. The only other report of an *E. soli* infection was in farmed fish in Malaysia. It is not known whether *E. soli* poses a risk for platelet transfusions. Prior to this study, there were no published data on pathogen reduction efficacy for *E. soli*.

**AIMS**: The aim of this study was to assess the inactivation of *E. soli* alone and in combination with *L. adecarboxylata* and *S. saprophyticus* in apheresis platelets using the INTERCEPT Blood System for Platelets.

**METHODS**: For the pathogen inactivation assessments, 335 mL of an apheresis platelet unit (35% plasma/65% platelets in PAS) was inoculated with 3.4 mL of an overnight culture of an individual bacterial species or a 1:1:1 (volume) mixture of *E. soli*, *L. adecarboxylata*, and *S. saprophyticus*. The contaminated platelet component was connected to an INTERCEPT Dual Storage Platelet Processing Set dosed with amotosalen and illuminated with target dose of UVA light. The unit was then transferred to the compound adsorption device (CAD) container and incubated for 16 h at 22°C with agitation. After incubation, the unit was transferred into storage bags and held at 22°C with agitation. Samples were taken pre- and post-treatment, day 5, and day 7. Bacterial titer was measured by plating on LB agar. On day 7, potential residual bacteria were assessed by incubating the remaining unit with an equal volume of LB broth in a flask overnight at 37°C with agitation.

**RESULTS**: For the individual assessment of *E. soli*, 7.5 ± 0.1 log CFU/mL was inactivated with no detectable bacteria observed at post-treatment, 5- and 7-days post-collection. For the combination assessment to assess whether INTERCEPT could inactivate the combination of pathogens found in the unit, inactivation of *E. soli*, *L. adecarboxylata*, and *S. saprophyticus* were observed at 7.2 ± 0.1 log CFU/mL with no detectable bacteria post-treatment, on days 5 and 7.

**SUMMARY/CONCLUSIONS**: We confirm in this study that amotosalen/UVA treatment can effectively inactivate *E. soli*, *L. adecarboxylata*, and *S. saprophyticus* to levels below the limit of detection after treatment and throughout the 7-day storage period. This study highlights the efficacy of INTERCEPT at inactivating multiple bacteria in a single unit. Further studies are needed to understand the mechanism of contamination of units after treatment during the storage period.

# Initial Experience of Switching Pathogen Inactivation System With Extended Platelet Shelf Life

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**BACKGROUND**: After a first evaluation of the quality of platelets treated with two pathogen inactivation (PI) methods in 2021 combining either amotosalen and UVA light (A-UVA (INTERCEPT™ Blood System) or riboflavin and UV light (R-UV (MIRASOL™ PRT System)), the Luxemburgish Red Cross decided to use A-UVA to extend the storage time of platelets from 5 days (hours calculated) to the end of the 6th day after collection. The objective was to reduce the high percentage of outdated products and to ensure a higher level of self-sufficiency. The implementation of A-UVA had also required some process modifications, especially regarding apheresis platelet yield and concentration that were initially not in accordance with the process entry requirements.

**AIMS**: To assess the impact of the switch of PI method on several aspects: platelet quality, percentage of expired products, process organization, level of non-conformities.

**METHODS**: Several "routine QC parameters" such as platelet concentration, platelet yield, pH (22°C) and the percentage of outdated platelet products were analyzed and compared to the period during which R-UV method had been used with a platelet storage time limited to 5 days. Moreover, the age of the platelet products issued was compared between both periods in order to assess the impact of storage time extension. Two types of platelet products were tracked: platelet from pools derived from Reveos whole blood separation (Terumo BCT®) and from Trima apheresis platelet collections (Terumo BCT®).

**RESULTS**: QC results showed several statistical differences: in A-UVA platelet pools, the platelet yield and volume were lower while the platelet concentration was higher. Regarding the apheresis, all the A-UVA products (single and double donations) were statistically more concentrated for the same platelet yield. The storage time extension had an impact of the average age of the products issued, increasing from 2.73 to 4.03 days for apheresis platelets and from 3.31 to 4.26 for platelet pools.

The percentage of expired products has been reduced from 6.1 to 2.4% and from 29.6 to 20.4%, for apheresis and platelet pools, respectively. No increase of non-conforming products has been observed.

**SUMMARY/CONCLUSIONS**: The main impact related to the change of PI method was a higher platelet loss for the platelet pools, mainly due to the processing, especially the step of compound adsorption. This was not observed for apheresis products: some parameters of the Trima collection program were initially modified (increase of the platelet collection concentration) in order to compensate this loss. The lower volume of photoactive compound added to the product to illuminate (15.0 or 17.5 for AUVA vs 35.0 ml for R-UV) can explain the increase of platelet concentration. Even if the use of A-UVA implies a delay in the product release (additional steps) compared to the R-UV treatment, we didn't experience any shortage.

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| Platelet Pools | R-UV 4 components (n=631) | A-UVA 4 components (n=143) | R-UV 5 components (n=2602) | A-UVA 5 components (n=1192) |
|---|---|---|---|---|
| Mean Platelet Yield 10e11/bag | 3.15 | 2.82 | 3.51 | 3.23 |
| Mean Platelet Concentration 10e9/l | 978 | 1011 | 874 | 899 |
| Mean Platelet Volume in ml | 322 | 280 | 401 | 360 |
| **Apheresis Platelets** | **R-UV single donation (n=607)** | **A-UVA single donation (n=453)** | **R-UV double donation* (n=384)** | **A-UVA double donation (n=184)** |
| Mean Platelet Yield 10e11/bag | 3.08 | 3.11 | 2.80 | 2.78 |
| Mean Platelet Concentration 10e9/l | 951 | 1144 | 945 | 1494 |
| Mean Platelet Volume in ml | 323 | 272 | 296 | 186 |

*After splitting, product characteristics are considered as "equivalent"

# Transfusion of Amotosalen-UVA Pathogen Reduced Platelet Components to Mature and Premature Neonatal Infants

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**BACKGROUND**: Platelet components (PC) prepared with amotosalen-UVA (A-UVA) pathogen reduction (PR) are indicated to reduce the risk of transfusion-transmitted infections (TTI) and transfusion-associated graft versus host disease (TAGVHD). PRPC (INTERCEPT™, Blood System, Cerus BV, Amersfoort, Netherlands) were mandatorily implemented in Switzerland in 2011 for all patients. Clinical data on neonates are sparse.

**AIMS**: We reviewed the use of PRPC for treatment and prophylaxis of bleeding in neonates before and after implementation of PRPC with a focus on concurrent PC transfusion and phototherapy for neonatal jaundice.

**METHODS**: A retrospective review of hospital records for premature and term neonates (0-28 days old) transfused with PC was conducted for two cohorts: patients receiving conventional PC (CPC) in 72 months before (2005-2010) and PRPC in 57 months after (2011-2015) PRPC implementation. The standard transfusion thresholds for premature and term nonbleeding neonates were < 50 x $10^9$/L and < 30 x $10^9$/L, respectively. CPC were stored for up to 5 days and irradiated prior to transfusion. PRPC were not gamma irradiated and stored up to 7 days. Medical records were audited for: gestational age, birth weight, phototherapy, indication for PC transfusion, PC transfusions, pre-transfusion platelet count, posttransfusion platelet count, count increment, phototherapy treatment, and adverse events related to transfusions associated with phototherapy. P-values for the treatment difference are based on Fisher's Exact test and a 1-way ANOVA model, respectively, for categorical and continuous variables.

**RESULTS**: 100 neonates received 234 PRPC and 91 received 171 CPC. In both cohorts, patients were dosed with 5 mL/kg of PC. PC platelet content was not measured at transfusion, but pre and post transfusion (1-4 hour) patient platelet counts were measured. Similar proportions of patients in each cohort had bleeding (central nervous system 18% vs 19%, lung 3% vs 3.3%) as the indication for PC transfusion. All other PC transfusions were prophylactic. The average gestational ages and birth weights were similar between cohorts. There were no substantial differences in the numbers of PC or FFP transfusions, but more RBC transfusions were reported in the CPC cohort. Similar proportions of patients required phototherapy in both periods (51%). Including the number phototherapy treatments as a covariate did not impact the observed difference in RBC transfusions between cohorts. Platelet count increments were within therapeutic ranges in both cohorts. No differences in adverse events related to PC transfusion and concurrent phototherapy were reported.

**SUMMARY/CONCLUSIONS**: The data support the efficacy and safety of PRPC in neonates who require concurrent platelet transfusion and phototherapy for jaundice.

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| n = Patients With Data: Mean ± SD | PRPC (n = 100) | CPC (n = 91) | P-value |
|---|---|---|---|
| Gestation age (weeks) | 32.8 ±5.3 n = 93 | 32.5 ± 5.0 n = 84 | 0.699 |
| Birth weight (Kg) | 1.8 ± 1.1 n = 100 | 1.8 ± 1.1 n = 91 | 0.649 |
| Age at phototherapy initiation (days) | 2.2 ± 2.9 n = 49 | 2.1 ± 2.6 n = 41 | 0.950 |
| Number of phototherapies | 3.8 ± 3.0 n = 51 | 2.3 ± 1.3 n = 46 | 0.002 |
| Bleeding prior to first PC transfusion (%) | 21% | 22% | 0.901 |
| Number of PC transfusions | 2.3 ± 2.9 n = 100 | 1.9 ± 1.2 n= 91 | 0.162 |
| Pre transfusion platelet count ($10^9$/L) | 53.2 ± 48.9 n = 100 | 42.5 ± 30.1 n = 91 | 0.074 |
| Post transfusion platelet count ($10^9$/L) | 130.4 ± 45.5 n = 100 | 137.8 ± 58.8 n = 91 | 0.330 |
| Platelet count increment ($10^9$/L) | 82.5 ± 45.0 n = 100 | 96.4 ±53.0 n = 91 | 0.052 |

# Pathogen-Reduced, Cryopreserved Platelets to Maintain Individual Platelet Support

**Z Przybylska[1], D Piotrowski[1], M Picard-Maureau[2]**

*1. Warsaw Regional Blood Transfusion Center, Warsaw, Poland; 2. Cerus Europe B.V., Amersfoort, Netherlands*

**BACKGROUND**: Providing adequate platelet (PLT) support for donors requiring cross-matched or HLA-typed platelets could be challenging, especially during holiday seasons. Cryopreservation of platelet concentrates (PCs) is a potential solution to overcome shortages and maintain platelet support. In our institution, we prepare cryopreserved PLTs from pathogen reduced platelets (CPRPs) to increase blood safety. It is known that cryopreservation of platelets induces a higher level of basal activation, lower level of activatability, increased clot formation time (CFT) and reduced clot firmness (MCF). That may lead to reduced post-transfusion recovery, but was reported not to impact hemostasis. It also was reported elsewhere that pathogen reduction treatment did not significantly impact these parameters additionally in cryopreservation procedures. Polish guidelines require a platelet count of $\geq 3x10^{11}$ per unit and a white blood cell (WBC) count of $<1x10^{6}$ per unit pre-freezing, and a recovery of >40% of platelets and a volume of 50-200 mL post thawing.

**AIMS**: Aim of the study was the assessment CPRPs manufacturing data and quality compliance with Polish guidelines, based on 2020-2022 data.

**METHODS**: Leukoreduced apheresis platelet concentrates (APCs) were collected with an Amicus® device (Fresenius) in 65% SSP+ (Macopharma) and 35% plasma followed by pathogen inactivation treatment with amotosalen/UVA (INTERCEPT® Blood System, Cerus). The APCs were pelleted in a centrifuge, reconstituted in 100 mL autologous plasma with 5% DMSO and subsequently frozen at -80°C (1 year shelf life) within 24 h post collection. The CPRPs were thawed at 37°C in a water bath, washed gently with 100 mL washing solution (SSP+, pH 6.5 with 2.5 mL ascorbic acid), pelleted in a centrifuge and reconstituted in 100 mL autologous plasma (post-thawing shelf-life 2 h). PLT and WBC counts were determined with an XN-550 hematology analyzer (Sysmex). The procedure was developed and validated solely by the Warsaw Regional Blood Donation Center independently.

**RESULTS**: 13.587 PCs were collected in 2020, 298 of them (2.2%) were cryopreserved. 14.884 PCs were collected in 2021, 282 of them (1.9%) were cryopreserved. 15.426 PCs were collected in 2022, 260 of them (1.7%) were cryopreserved. 290 CPRPs were thawed and distributed in 2020, 284 in 2021 and 249 in 2022. Data from 156 CPRPs were included in this study to obtain representative results (approx. 20% of annual production). The WBC count of all APCs was $<1x10^{6}$/unit pre-cryopreservation, the average PLT count was $3.4x10^{11} \pm 0.6$, post-cryopreservation $2.3x10^{11} \pm 0.5$ (average recovery rate 68.5% ± 10.5 (40.4-97.8)). The average volume post-thawing was 102.2 mL ± 4.5 (90-117). No CPRP transfusion-related adverse events were reported.

**SUMMARY/CONCLUSIONS**: We recognized a trend for a decreased demand for CPRPs from 2020 to 2022, which may be explained by the stepwise cessation of pandemic measures, releasing restrictions for blood donors. CPRPs are used only when fresh PCs are not available as safety pool to ensure platelet availability for donors requiring HLA typed/crossmatched platelets in holiday/vacation seasons with limited availability of donors. CPRP fulfilled Polish quality requirements, the recovery rate was in line with previous published data (70.6% in *Sandgren*, *Blood Transfus*, 2022).

# Inactivation of WHO Reference Bacterial Strains in Platelet and Plasma Components Using Amotosalen/UVA Treatment

**P Nahata[1], M McCormack[1], A Johnson[1], B Stafford[1], M Krath[1], P Bringmann[1], T Lu[1]**

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**BACKGROUND**: The INTERCEPT® Blood System for platelets and plasma utilizes amotosalen and UVA light to efficiently inactivate a wide range of pathogens and leukocytes in platelet concentrates (PC) and plasma. The INTERCEPT Blood System for platelets 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-3/35% plasma). The INTERCEPT Blood System for Plasma is available both in Europe and US. The World Health Organisation (WHO) Expert Committee on Biological Standardisation (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*, Vox Sanguinis, 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% PAS-3/35% 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 (INTERCEPT Blood System for Platelets – Dual Storage (DS) Processing Set). Human plasma donations were collected and pooled to yield individual units of ~650 mL (INTERCEPT Plasma Processing Set). Four replicates per platelet matrix were performed for each PEI strain of transfusion-relevant bacteria, including *K. pneumoniae* and *S. aureus* in plasma, with each replicate consisting of one unit spiked with a single PEI strain. The contaminated PC and plasma units were then treated with amotosalen and UVA light in the INTERCEPT Blood System for platelets and plasma, respectively. ~5 mL and ~50 mL samples were taken pre- and post- UVA treatment, respectively and were analyzed for bacterial titer by plating on appropriate media (100µL – 10mL/plate).

**RESULTS**: Platelet and plasma units contaminated with PEI bacterial strains (**Table 1**) were treated with amotosalen and UVA in the INTERCEPT Blood System for platelets and plasma, respectively. Robust bacterial inactivation was observed post-treatment (**Table 1**).

**SUMMARY/CONCLUSIONS**: The INTERCEPT Blood System for Plasma consistently inactivated high titers of *K. pneumoniae* and *S. aureus*. The INTERCEPT Blood System for Platelets efficiently inactivated *K. pneumoniae*, *S. aureus*, *E. coli* and *S. epidermidis*. These data demonstrate that the INTERCEPT Blood System for platelets and plasma robustly inactivates WHO standardized bacteria strains associated with TTBI.

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**Table 1: Bacterial Inactivation Using Amotosalen/UVA Treatment for Human Plasma and Platelet Concentrates in 100% Plasma and 65% PAS-3/35% Plasma**

| Bacteria (Strain) | Matrix | Log Reduction* (Log cfu/mL) |
|---|---|---|
| *K. pneumoniae* PEI-B-P-08 | PC In 100%plasma | 4.7±0.4 |
| *K. pneumoniae* PEI-B-P-08 | PC In 65% PAS-3/35% plasma | 5.6±0.2 |
| *K. pneumoniae* PEI-B-P-08 | Human plasma | 4.5±0.5 |
| *S. aureus* PEI-B-P-63 | PC In 100% Plasma | 6.7±0.0* |
| *S. aureus* PEI-B-P-63 | PC In 65% PAS-3/35% plasma | 7.6±0.1* |
| *S. aureus* PEI-B-P-63 | Human plasma | 6.5±0.1* |
| *E. coli* PEI-B-P-19 | PC In 100% Plasma | 7.4±0.2* |
| *E. coli* PEI-B-P-19 | PC In 65% PAS-3/35% plasma | 7.2±0.1* |
| *S. epidermidis* PEI-B-P-06 | PC In 100% Plasma | 7.7±0.1* |
| *S. epidermidis* PEI-B-P-06 | PC In 65% PAS-3/35% plasma | 7.8±0.0* |

* No residual bacteria were detected at post- UVA treatment.

# Pathogen Reduced Plasmas from Maxi-Pools Combined With Fast Thawing for Use In Emergency Situations

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**BACKGROUND**: Early and timely use of transfusions has effect on survival in trauma setting. Transfusion packs containing 4 units of erythrocytes, 4 units of plasma and 1 platelet unit have been adopted in our institution for trauma patient care. This practice had a detrimental effect on the outdating of plasma. 25% of plasmas for transfusion were outdated in 2018. The plasma needed for the transfusion packs is thawed as soon as the order comes in, and the ward can return the unused units back to the blood bank. If there is no need for thawed plasma within 7 days after thawing, the plasmas are discarded. Clinicians also expressed a wish to have more standardized products with regards not only to volume but also content. We developed a 10-unit plasma pooling technique allowing to optimize the use of pathogen reduction (PR) processing sets and delivering 12 units of 200 mL end products subsequently fast-thawed before transfusion.

**AIMS**: To assess, based on plasma quality parameters tested *in-vitro*, a preparation procedure based on pools of 10 previously frozen plasma units subsequently split into volumes compatible with the process for PR treatment and thawed post-frozen storage with a fast thawer.

**METHODS**: 100 WB-derived leukocyte depleted plasma units were frozen within 24 hours at ≤25°C and stored for 7 days. After thawing, 10 maxi-pools of 10 A, B or AB plasma units were constituted. After splitting each into 4 sub-pools of 650 mL, they were PR treated using amotosalen and UVA (A-UVA, INTERCEPT® Blood System, Cerus). Further splitting into units of 3 results in a total of 120 PR plasma units at 200 mL. The units were frozen at ≤25°C for 1 week, then thawed either in a CS201 (Conroy) fast plasma thawer for 5 min or in other control devices (Barkey Plasmatherm and Sahara, 17 to 23 min). Factor VIII, Fibrinogen, Albumin, IgG, Protein S, and vWF were measured in plasma units, maxi-pools, and plasmas after PR treatment and thawing.

**RESULTS**: Results of the assays in the **Table**, given at the different phases of the process.

**SUMMARY/CONCLUSIONS**: Pooling 10 plasma units before the PR treatment standardizes volume and protein content of plasma units. Besides the economic value of generating 12 products for transfusion, this procedure combined with a thawing time of about 5 minutes is of value in emergency situations and allowed to decrease outdating of plasmas to 12%.

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| Mean ± SD Parameter | Plasma units (N =100) | Maxi-pools of 10 units (N=10) | Plasma units after A-UVA PR, storage and thawing (N=20) | 7-day ≤25°C |
|---|---|---|---|---|
| | Frozen, thawed | Frozen, thawed | CS 201 | Control thawers |
| Factor VIII:C (IU/mL) | 1.07±0.3 | 1.08±0.1 | 0.72±0.07 | 0.69±0.08 |
| Fibrinogen (g/L) | 2.7±0.4 | 2.6±0.2 | 2.3±0.1 | 2.3±0.1 |
| Albumin (g/L) | 32.7±2.1 | 33.1±1.6 | 32.6±0.5 | 32.5±0.5 |
| IgG (g/L) | 8.66±1.57 | 8.63±0.52 | 8.42±0.52 | 8.44±0.50 |
| Protein S (IU/mL) | 0.94±0.17 | 0.94±0.05 | 0.84±0.08 | 0.84±0.05 |
| vWF (IU /mL) | 1.20±0.36 | 1.19±0.14 | 1.13±0.13 | 1.13±0.13 |

Factor VIII and fibrinogen levels were not significantly reduced after freezing and thawing procedures. However, after PR, there was a statistically significant ($p<0.05$) but still clinically acceptable reduction of these levels with 69% and 87% recovery for Factor VIII and fibrinogen, respectively. These concentrations are still over the recommended levels of ≥0.5 IU/mL and ≥2 g/L. Only Factor VIII was lower ($p<0.05$) using control devices versus the CS 201 fast thawer. Other studied proteins were not significantly affected in the processes.

# Amotosalen/UVA Light Pathogen Reduced Plasma from Previously Quarantined Units Stored for Two Years

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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 2-year stability of A-UVA PFP.

**METHODS**: 18 apheresis ACD-A plasmas of at least 640 mL were collected, split in three sub-units, frozen with 24 hours and stored at <-25°C for 30 weeks. After thawing, pools of triplets were reconstituted and submitted to the A-UVA treatment split in 3 units and frozen within 6 hours for <-25°C storage. Similarly 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-day frozen storage (post treatment), and at 1 year and 2 years from collection; total proteins, Albumin, Immunoglobulins, Coagulation factors and coagulation tests, coagulation inhibitors and fibrinolysis factors, thrombin generation test.

**RESULTS**: The results of a selection of plasma parameters for the 36 combined replicates are reported in the **Table** below (post treatment not shown). 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 clotting time. A sufficient stability of these parameters was observed over a 2-year storage period at ≤-25°C. This process can also be applied in first intention to optimize production efficiency by batch processing of frozen plasma units.

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| N=36 | Baseline (after 30-week ≤-25°C storage) | After thawing / A-UVA PR / & frozen storage up to 1-year from collection* | 2 years from collection* |
|---|---|---|---|
| Total proteins (g/L) | 62.9 ± 3.1 | 61.6 ± 3.4$^{s}$ | 60.5 ± 3.1$^{s}$ |
| PTT (%) | 95 ± 7 | 75 ± 5$^{s}$ | 75 ± 5$^{s}$ |
| Fibrinogen (g/L) | 2.81 ± 0.43 | 2.47 ± 0.36$^{s}$ | 2.51 ± 0.39$^{s}$ |
| FVIII (IU/mL) | 1.22 ± 0.29 | 0.83 ± 0.19$^{s}$ | 0.77 ± 0.18$^{s}$ |
| VWF Ag (IU/mL) | 1.11 ± 0.11 | 1.10 ± 0.10 | 1.07 ± 0.11$^{s}$ |
| AT-III (IU/mL) | 0.97 ± 0.07 | 0.99 ± 0.06$^{s}$ | 0.97 ± 0.06 |
| Protein C (IU/mL) | 0.97 ± 0.14 | 0.85 ± 0.13$^{s}$ | 0.83 ± 0.12$^{s}$ |
| Protein-S (IU/mL) | 0.84 ± 0.15 | 0.78 ± 0.13$^{s}$ | 0.72 ± 0.12$^{s}$ |
| $\alpha$2-antiplasmin (IU/mL) | 0.99 ± 0.07 | 0.81 ± 0.05$^{s}$ | 0.77 ± 0.05$^{s}$ |

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

# A Pilot Study Tracking Pathogen Reduced RBCs *In Vivo* Using Surface Acridine and Biotin Flow Cytometric Markers

**R J Benjamin[1], J P Pitman[1], M von Goetz[1], K Waldhaus[1], N Mufti[1], P E Zerra[2,3], R M Fasano[2,3], M E M Yee[2,4]**

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**BACKGROUND**: Pathogen reduction of red blood cells (PR-RBCs) with amustaline/glutathione is an investigational process designed to reduce transfusion-transmitted infection risk of RBC transfusions. Low titer antibodies specific for acridine (a breakdown product of the PR process) bound to RBC surfaces have been detected in a small number of naïve and exposed patients.

**AIMS**: We designed an *in vivo* RBC survival study to track PR-RBCs by flow cytometry using a monoclonal antibody specific for acridine-RBC adducts to measure RBC survival in a patient with sickle cell disease.

**METHODS**: The patient received three ~7 mL aliquots of different biotin dose labeled RBCs: Two aliquots drawn from one RBC unit before and after PR treatment (Pre-PR RBCs, 2 μg/mL biotin; PR-RBCs, 6 μg/mL biotin), and one from a conventional RBC unit (Control, 18 μg/mL biotin). The remaining unlabeled PR-RBC and Control RBC units were also transfused. Semi-quantitative flow cytometry for acridine and biotin was performed in triplicate on samples drawn at designated time points post-transfusion.

**RESULTS**: Flow cytometry for biotin labelling within 1 hour of transfusion detected 0.72% of PR-RBCs, 0.76% of Pre-PR RBCs and 0.92% of Control RBCs. The acridine assay detected 12.3% of circulating PR-RBCs representing the entire transfused unit. RBC surface biotin density declined slightly over 98 days: ~7,000-5,000 molecules/RBC at 18 μg/mL (Control); 2,500-2,000 molecules/RBC at 6 μg/mL (PR-RBCs); and 800-600 molecules/RBC at 2 μg/mL (Pre-PR RBCs). Acridine antigen density on RBC surfaces (**Table**) was approximately equivalent to the 18 μg/mL biotin label within 1 hour of transfusion. Acridine density declined ~55% at 24 hours post-transfusion and by ~87% on day 7 with elution of acridine in a uniformly monotonic fashion suggesting that no RBCs completely lost the acridine label. Acridine labeling remained detectable throughout the 98-day observation period. The shapes of RBC survival curves for both biotin and acridine labeled cells were similar over 98 days. Screening for antibodies to acridine and to biotin-RBCs were negative throughout the survival study.

**SUMMARY/CONCLUSIONS**: PR-RBC survival can be tracked *in vivo* by flow cytometry for RBC surface acridine with similar sensitivity as biotin labeling. Acridine labels allow PR-RBC tracking *in vivo* without extra processing. Acridine antigen density on PR-RBCs declines rapidly and uniformly and stabilizes at ~8-13% of the transfused level within 7 days. Low residual acridine levels on RBC surfaces may account for the lack of laboratory evidence of hemolysis with low titer treatment-emergent antibodies to PR-RBCs seen in clinical studies. Additional research is needed to confirm this hypothesis.

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**Table: Detection of Acridine Surface Antigen**

| Day | Acridine molecules/RBC | % Acridine positive RBCs |
|---|---|---|
| 0 (≤ 1-hr) | 8,414 | 12.30 |
| 1 | 3,764 | 12.60 |
| 7 | 1,360 | 11.20 |
| 14 | 1,417 | 11.00 |
| 25 | 1,039 | 7.10 |
| 54 | 946 | 3.40 |
| 67 | 760 | 1.80 |
| 82 | 649 | 0.50 |
| 98 | 643 | 0.10 |

The INTERCEPT Blood System for Red Blood Cells is in development and not approved for commercial use.

## 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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Use of INTERCEPT Plasma or Platelets is contraindicated in patients with a history of allergic response to amotosalen or psoralens.
Consult instructions for use for indications, contraindications, warnings, and precautions.