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Pathogen-reduced buffy coat platelets

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Primary target audiences: transfusion medicine physicians, non-transfusion medicine physicians, nurses, medical laboratory technologists in a hospital laboratory.

The purpose of this article is to provide information about pooled platelets psoralen-treated (PPPT), a new blood product introduced by Canadian Blood Services in January 2022. This article provides information about the PPPT production process and the technology used to inactivate pathogens. It also compares PPPT to untreated platelets in terms of product characteristics, benefits and drawbacks.

Introduction

Blood components can become contaminated with bacteria from the skin of donors during blood donation or, less often, from the donor's blood stream.[1,2] Platelet units in particular face a greater risk of bacterial contamination because they are stored at room temperature. Unpublished Canadian Blood Services surveillance data from 2006-2016 showed that bacterial sepsis occurred in 1 in every 125,000 transfused platelet concentrates.[3]

A pivotal study published in 2006 highlighted a need for better surveillance methods for detecting platelet bacterial contamination. In the study, a university hospital transfusion service cultured platelet units issued to patients over 10 years, including some supplemental gram stain, pH measurements, and early 24-hour cultures of apheresis platelets. Surveillance detected bacteria in 1:418 random-donor platelet units (pools of 5 units) and in 1:2,213 of apheresis platelets.[4] The authors then compared the bacterial growth that occurred after the transfusion was completed with signs and symptoms of bacterially contaminated platelets even if no transfusion reaction was reported. They correlated the severity of a transfusion reaction with >105 colony forming units. The study found that 13 of 32 patients who had been transfused with contaminated platelets had transfusion reactions, including 9 severe reactions and 3 deaths.

These findings accelerated the implementation of additional bacterial contamination mitigation strategies at Canadian Blood Services, including the introduction of diversion pouches used during whole blood collection[5] and large volume delayed bacteria culture sampling.[6] Implementation of an enhanced large volume bacterial detection screen algorithm resulted in a threefold reduction in septic transfusion reactions reported by hospitals.[6]

At Canadian Blood Services, untreated platelets (i.e., those that have not been pathogen-reduced) are routinely screened for bacterial contamination using microbial culture methods of the BACT/ALERT® 3D system, although low initial inoculum levels may result in sampling error or be below the threshold of detection, even after 7 days of incubation.[6] For more information on platelet bacterial testing see our FAQ: Canadian Blood Services platelet bacterial testing.

Despite significant gains in prevention, bacterial contamination of blood components remains higher than the risk of other transfusion-transmitted infections.[1] To ensure the safety of their blood supply, some countries have approved pathogen inactivation technologies to address the risk of bacterial transmission through blood components.[1, 7]

Pathogen inactivated platelets

In December 2021, Health Canada approved the use of Cerus INTERCEPT™ Pathogen Inactivation Technology for manufacturing pooled platelets psoralen-treated (PPPT) at Canadian Blood Services. This technology serves to further reduce the risk of pathogen transmission to transfusion recipients by inactivating pathogens, including:

- Viruses (enveloped and non-enveloped)
  - Including HIV-1, cell-associated, HTLV-I/II, West Nile virus, chikungunya virus, cytomegalovirus (CMV), influenza A virus
- Bacterial contamination (gram-positive, gram-negative organisms and spirochetes)
  - Including *Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus, Treponema pallidum* (syphilis), *Borrelia burgdorferi* (Lyme disease)
- White blood cells (leukocytes)
  - Human T cells
- Protozoan parasites
  - Including *Plasmodium falciparum, Babesia microti, Trypanosoma cruzi*

Active Compound of the Cerus INTERCEPT™ Pathogen Inactivation Technology: Amotosalen

Mechanism of action

The INTERCEPT™ inactivation technology utilizes a photoreactive compound known as amotosalen S-59 (amotosalen), which is a synthetic psoralen. Psoralens are compounds that intercalate within nucleic acids that compose the DNA and RNA of organisms and viruses. Amotosalen S-59 is incorporated into platelet components through a specialized process and becomes activated when exposed to ultraviolet A (UVA, 320–400 nm) illumination, causing permanent crosslinking between nucleic acid strands. Crosslinking damages DNA and RNA, which inactivates viruses, bacteria, protozoa and leukocytes that may contaminate platelet units. Amotosalen does not exhibit specificity towards the genomic material of any particular organism or nucleic acid sequences. Thus, any cellular material with DNA or RNA is modified by amotosalen, including donor-derived platelets and white blood cells. The inactivation of genetic material in donor platelets does not affect platelet activation or function.

After the addition of amotosalen and illumination with UVA light, platelets are transferred to a bag containing a compound adsorption device (CAD) that removes residual amotosalen and its free photoproducts, and the bag is agitated for 6 to 16 hours. The material in the compound adsorption device decreases the amotosalen from 150 µmol/L to 0.5 µmol/L post-adsorption.[8]

Pathogen inactivation efficacy

Amotosalen was studied with enveloped and non-enveloped viruses, gram-negative and gram-positive bacteria, and parasites. The infectious disease burden is measured as the log reduction from the original spiked inoculum. The efficacy varies by organism, with most pathogen reduction occurring at greater than 3 log.

Table 1: Efficacy of INTERCEPT™ inactivation technology on viruses, bacteria and parasites in PAS‡

Enveloped viruses	Log reduction	Non-enveloped viruses	Log reduction
HIV-1, cell free	≥5.6	HAV+	0
HIV-1, cell-associated	≥5.4	Parvo B19+	>6.2
HBV	≥4.8	Blue tongue virus	5.2
HCV	≥4.1	Human adenovirus	≥4.9
HTLV-I	4.7	Calicivirus	2.1
HTLV-II	≥5.1		
Cytomegalovirus	≥4.9		
Bovine viral diarrhea virus+	>6.0		
West Nile virus	≥6.3		
Chikungunya	≥5.7		
Influenza A virus	≥5.9		
SARS-CoV-2*	>3.31		
Dengue virus†	>5.2		
Crimean-Congo hemorrhagic fever virus+	2.9		
Gram-positive bacteria	**Log reduction**	**Gram-negative bacteria**	**Log reduction**
Bacillus cereus (incl. spores)	3.7	*Escherichia coli*	>6.3
Bacillus cereus (vegetative)	≥5.5	*Enterobacter cloacae*	6.6
Bifidobacterium adolescentis	≥6.0	*Klebsiella pneumonia*	>6.2
Clostridium perfringens (vegetative)	≥6.5	*Pseudomonas aeruginosa*	≥6.7
Corynebacterium minutissimum	≥5.3	*Salmonella cholerasuis*	>6.2
Listeria monocytogenes	≥6.3	*Serratia marsescens*	≥6.7
Proprionobacterium acnes	≥6.5	*Yersinia enterocolitica*	>5.9
Staphylococcus aureus	≥6.6		
Staphylococus epidermidis	≥6.4		
Streptococcus pyogenes	≥6.8		
Lactobacillus species+	>6.9		
Parasites	**Log reduction**	**Spirochetes**	**Log reduction**
Babesia microti	≥4.9	*Borrelia burgdorferi*	≥6.8
Leishmania major+	>4.3	*Treponema pallidum*	≥6.4
Leishmania mexicana	≥5.0		
Plasmodium falciparum	≥6.6		
Trypanozoma cruzi	≥7.8		

† Schlenke P. Pathogen inactivation technologies for cellular blood components: an update. *Transfus Med Hemother*. 2014;41(4):309-325.
* Hindawi SI, El-Kafrawy SA, Hassan AM, et al. Efficient inactivation of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in human apheresis platelet concentrates with amotosalen and ultraviolet A light. *Transfus Clin Biol*. 2022;29(1):31-36. doi:10.1016/j.tracli.2021.08.005
‡ Cerus website. https://intercept-usa.com/what-is-intercept/intercept-platelets/broad-spectrum-pathogen-reduction/

Safety profile of amotosalen

The toxicity of psoralen-based treatments has been extensively studied. The toxicity of the INTERCEPT pathogen inactivating agent, amotosalen, was evaluated in Phase I/II trial data of escalating doses of INTERCEPT platelets and measured amotosalen levels.[9] A 1000-fold safety margin based on animal studies is often required before human studies are conducted: a 10-fold margin to account for animal to human

physiology extrapolation, another 10-fold margin to account for human physiologic variations, and an additional 10-fold margin to detect the variability in all toxicology endpoints.[10] The maximal safety margin of amotosalen is estimated to be 150,000 and 30,000 times higher in rats and dogs than humans, respectively, based on a single transfusion of INTERCEPT treated platelets.[9] For context, the safety margins of over-the-counter medications are much lower; the safety margin of acetaminophen is only 100-fold. Mouse models exposing a fetus to high concentrations of amotosalen showed no growth abnormalities.[11] Additionally, amotosalen is water soluble and rapidly excreted. Thus, trace amounts of the compound in blood components will not bioaccumulate.[2]

Platelet additive solution

Platelet additive solution (PAS) is designed to replace a portion of plasma contained within platelet units. During the buffy coat pooling process and before amotosalen treatment, PAS is added to the platelet pool. The PAS solution utilized with the INTERCEPT™ system is the Macopharma SSP+. It contains sodium citrate dihydrate 3.18 g, sodium acetate trihydrate 4.42 g, sodium dihydrogen phosphate dihydrate 1.05 g, disodium phosphate anhydrous 3.05 g, potassium chloride 0.37 g, magnesium chloride hexahydrate 0.30 g, sodium chloride 0.37 g, magnesium chloride hexahydrate 0.30 g, and sodium chloride 4.05 g per 1000 mL of water. SSP+ is relatively inert compared to plasma. The final ratio of SSP+ to plasma in PPPT is about 60:40.

Production of pooled platelets psoralen-treated

The production of PPPT begins with the collection of whole blood from donors in a Canadian Blood Services donor centre. Whole blood units are centrifuged to separate out the plasma, buffy coat (containing leukocytes and platelets) and red blood cells, similar to the centrifugation method used for whole blood buffy coat collections (also referred to as the B1 method). Seven buffy coats—one from each donor unit— are then pooled together and PAS is added. The buffy coat pool is then centrifuged and the platelet-rich supernatant is extracted from the remaining buffy coat red blood cells through a platelet-sparing leukoreduction filter.

Amotosalen is then added to the seven-pool platelet unit, which undergoes treatment with UV illumination to facilitate crosslinking between any residual nucleic acid material within the unit. A single treatment with UVA can adequately intercalate DNA and RNA from donor cells and pathogens within a range of concentrations. Residual amotosalen and its photoproducts are then removed via the use of a CAD. The double-dose PPPT unit is then split into two single-dose PPPT units as they are transferred into storage containers use.

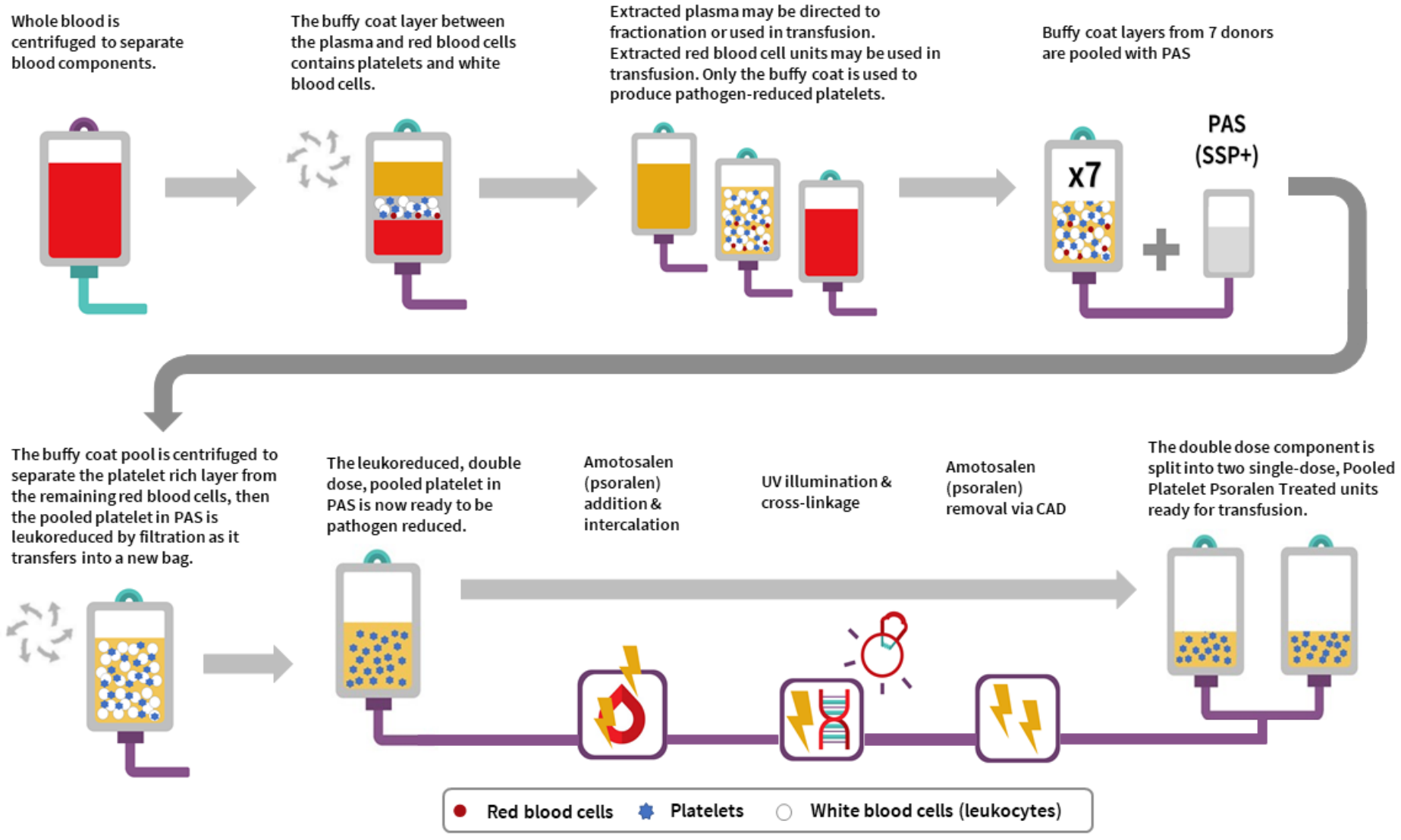

Figure 1: PPPT manufacturing at Canadian Blood Services.

Product characteristics

The volume per unit of PPPT is approximately 184 +/- 9 mL.[3] In comparison, the volume per unit of untreated pooled platelets is 317 +/- 16 mL.[12]

The platelet yield of PPPT is 251 +/- 32 x 10^9 platelets/unit.[3] In comparison, untreated pooled platelets have an average platelet yield of 339 (+/- 44) x 10^9 platelets/unit.[12]

The platelet count of PPPT is of 1,363 +/- 188×10^9 platelets/L. In comparison, the platelet count of untreated pooled platelet products is 1,070 x 10^9 platelets/L.

The residual white blood cell count post-filtration in a double-dose unit of PPPT is 0.04 +/-0.06 x 10^6cells/unit, compared with the residual white blood cell count post-filtration in untreated pooled platelets of 0.0427 +/- 0.09 x 106/unit. Additionally, the few residual white blood cells in PPPT are inactivated by amotosalen.

Pathogen-reduced platelets are manufactured from seven male or female donor buffy coats, which are pooled together to create an individual double-dose unit that is then divided into two separate units. In comparison, untreated pooled platelet units are created with buffy coats from up to three individual female donors and one male donor.

While PPPT are derived from more donors (seven donors) than untreated pooled platelets (four donors) the total volume of plasma in unit of PPPT is less than a unit of untreated pooled platelets. The ratio of plasma to PAS in PPPT is approximately 40:60. The average plasma volume anticipated in PPPT is expected to be 75 +/- 4 mL (11 mL per donor), compared to 327 mL total volume in untreated pooled platelets (20 mL from each of three donors plus 267 mL from a male donor).

Table 2: Characteristics of untreated pooled platelets, pooled platelet psoralen-treated, and untreated apheresis platelets.

Characteristic	Untreated Pooled Platelet	Pooled Platelet Psoralen-Treated	Untreated Apheresis Platelet
Mean unit volume (mL)	317	184	223
Number of donors in component	4	7	1
Mean plasma volume (mL)	317 (approximately 20 mL for 3 donors and + 257 mL plasma from one male donor)	75 (approximately 11 mL per donor)	173
Approximate platelet count (x109 platelets per L)	1,069	1,363	1,493
Resuspension solution	Plasma	Approx. 60% Platelet Additive Solution (PAS-E) – 40% Plasma	Plasma
Anticoagulant	CPD	CPD	ACD-A

Characteristic	Untreated Pooled Platelet	Pooled Platelet Psoralen-Treated	Untreated Apheresis Platelet
Bacterial screening performed by Canadian Blood Services	Yes	No	Yes
Typical time to release component to hospital after blood collection from donor	Day 3	Day 2	Day 3
Component shelf life (from day of blood collection)	7 days	5 days	7 days
Viable lymphocytes present?	Yes, irradiation required for vulnerable patients	Viable lymphocytes not present, irradiation not required for vulnerable patients	Yes, irradiation required for vulnerable patients

Packaging and labeling

PPPT are stored in gas-permeable ethylene vinyl acetate bags. These bags do not contain any di-ethyl hexyl phthalate (DEHP) plasticizer; however, the attached transfusion ports and tubing may be made of plastics that contain DEHP. Platelet units may also come into contact with DEHP plasticizer during collection and product manufacturing.

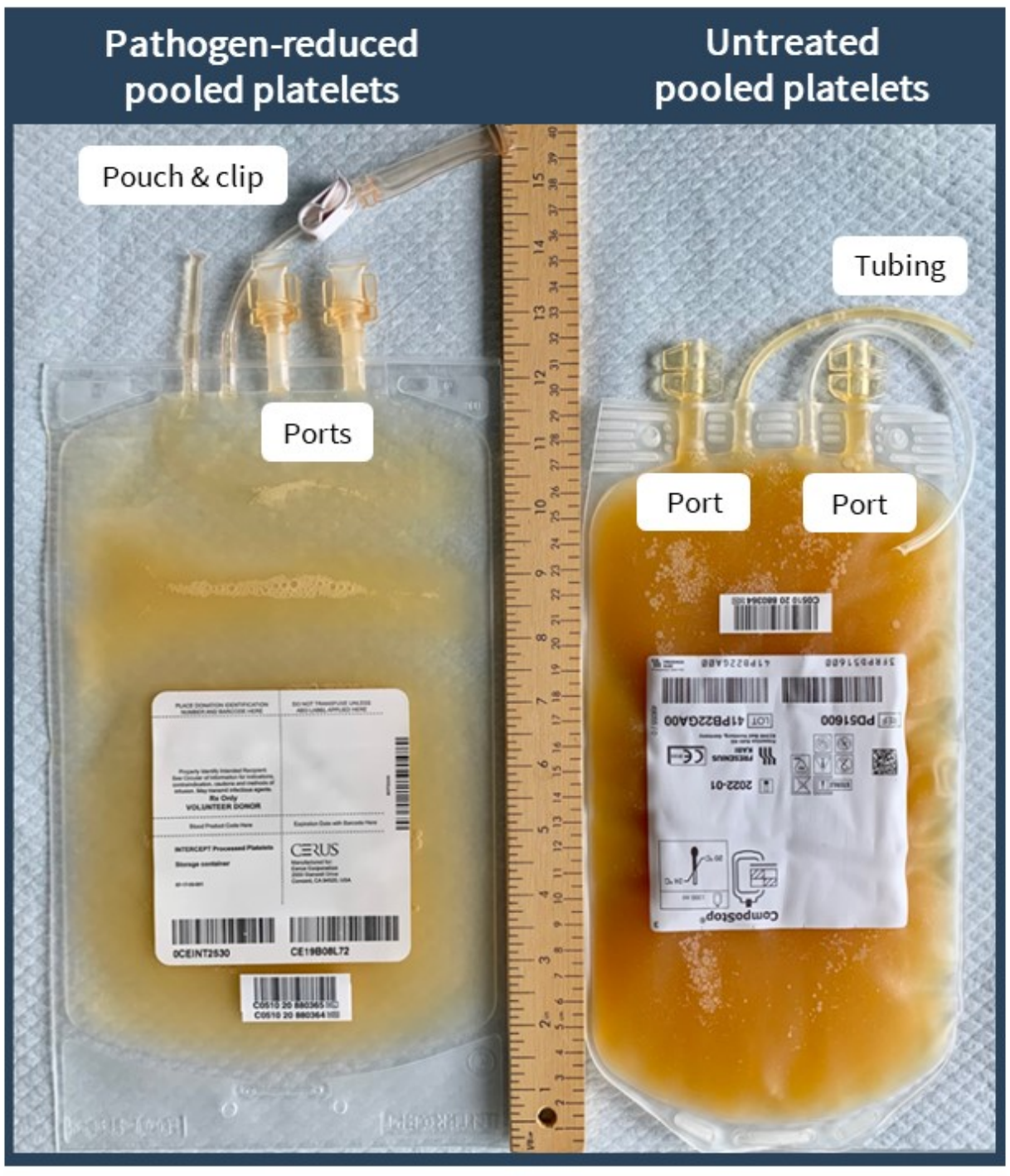

Figure 2: PPPT (left) and untreated pooled platelet (right) bags.

The size of PPPT bags is larger (31 x 18 cm) than bags used for untreated pooled platelets (30 x 15 cm). In addition to two transfusion ports, the untreated pooled platelets bag has pigtail tubes, one of which may be used for sampling, and the new PPPT bag has an integrated sampling pouch rather than pigtail tubing.

Benefits

Amotosalen

PPPT are associated with multiple patient benefits compared to untreated platelets, including reduced bacterial contamination, decreased risk of transfusion-transmitted infections, inactivation of white blood cells, and reduced risk of adverse effects from plasma transfusion. In addition, because pathogen-reduction eliminates the need for PPPT to undergo bacterial testing, as is currently performed on untreated platelets, PPPT are released approximately 24 hours before untreated platelets (see Figure 3).

Component	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Untreated	Collected	Produced	BacT tested	Released Available for distribution to hospitals				
Psoralen treated			Released Available for distribution to hospitals				N/A	N/A

Figure 3: A comparison of platelet release timelines for untreated and pathogen-reduced pooled platelets.

Evidence from Switzerland supports the safety and efficacy of the INTERCEPT pathogen inactivation procedure. Hemovigilance data shows that after implementation of pathogen inactivation in 2011 until 2016, there were no reports of transfusion-transmitted bacterial infection.[13] In contrast, between 2005 – 2011, prior to implementation of pathogen inactivation, there were 16 cases of transfusion-transmitted bacterial infections. Another study analysed 19,175 pathogen-reduced platelet transfusions across 21 centres in 11 countries and identified no cases of transfusion-transmitted infection, further supporting the safety profile of INTERCEPT-treated platelets.[14]

Pathogen inactivation provides an additional layer of safety for platelet components, and complements the donor selection criteria (see Chapter 6 of the Clinical Guide to Transfusion) and pre-transfusion pathogen testing performed on all donations (see Chapter 8 of the Clinical Guide to Transfusion). Infectious disease testing will continue as part of Canadian Blood Services' blood donor screening process; however, bacterial testing with the BACT/ALERT® 3D system is not required for PPPT. The efficiency of amotosalen inactivation varies by pathogen, and some level of protection may also be provided against emerging blood borne pathogens.

The inhibition of leukocyte replication and cytokine production is also an important benefit of the Cerus INTERCEPT™ Pathogen Inactivation Technology because it simplifies platelet inventory management and ordering. Because amotosalen treatment prevents T cell proliferation, irradiated platelet units for preventing transfusion-associated graft versus host disease are no longer needed.[15] Similarly, the need for cytomegalovirus (CMV)-negative blood components, although already limited, is removed because PPPT is considered to be CMV-negative.[16]

Some pathogens are resistant to the treatment using amotosalen, such as hepatitis A, hepatitis E, poliovirus, parvovirus B19, and prions, the agent of variant Creutzfeldt-Jacob disease. In addition, some limitations in the efficacy of the technology have been raised.[17] Although amotosalen is added in excess in order to achieve published log reductions in infectious agents, there is a possibility that pathogen inactivation may be incomplete if there is a large pathogen burden, poor light energy delivery due to interfering substances, or potential human error during blood processing.[17]

Platelet additive solution

The use of PAS dilutes plasma antibodies and anticoagulant used in the collection of whole blood. The presence of PAS also reduces the incidence of allergic reactions and febrile non-hemolytic transfusion reactions.[18-20] In a subgroup analysis of a pediatric study, a lower rate of mild allergic reactions was found when PAS was added to the PPPT.[19, 21]

The small amount of plasma present in PPPT decreases titres of anti-A, anti-B, and anti-AB. However, Canadian Blood Services cannot make any claims about the final antibody titres.

Clinical efficacy

INTERCEPT™ treated platelets have been transfused without a single reported culture confirmed case of bacterial contamination.[22] Safety endpoints from clinical trials and published hemovigilance data demonstrated no statistically significant change in serious adverse events, including thromboembolism and anaphylaxis (risk ratio 1.09 [0.88 - 1.35]), acute transfusion reactions (risk ratio 0.96 [0.75 - 1.24]), or other adverse events (risk ratio 1.01 [0.97 - 1.05]) in clinical trials and cohort studies.[14, 23]

The safety and efficacy of the PPPT have been demonstrated in pediatric patients,[21, 24, 25] and neonates as well.[26] Schulz and colleagues reported a safety monitoring assessment on the use of pathogen-reduced platelet products in pediatric patients in a tertiary medical centre between November 2016 and July 2018.[24] Their cohort of 1,932 platelet transfusions in 240 patients included conventional platelet and pathogen-reduced products with a ratio of 45% to 55% because the use of PPPT represented most of the platelet transfusions by November 2017. No differences in red cell utilization and transfusion reactions were reported. A second study reviewing only PPPT transfusion in 191 patients less than 18 years of age over 300 days found no difference in transfusion rates of or acute adverse events.[27]

A phase IV post-market surveillance study, the PIPER trial, evaluated platelet transfusions of hematology-oncology patients at 15 U.S. sites. The study evaluated 2,291 patients (9% were less than 18 years of age) over 10,767 platelet transfusions and found no difference in treatment-emergent assisted mechanical ventilation or pulmonary injury between both types of platelet transfusion, and no significant difference was detected for ARDS or adverse events.[28]

Drawbacks

Non-immune platelet refractoriness

Many of the clinical trials using INTERCEPT platelets studied frequently transfused patient populations, including haematology-oncology patients. The studies were inconsistent in the types of pathogen-reduced platelet manufactured (e.g., plasma only, PAS, pooled platelets, apheresis platelets). However, overall, there was a statistically significant increase in platelet transfusions for patients who received pathogen-reduced platelets compared to those who received untreated platelets as measured by the corrected count increment (CCI) at one hour and 24 hours following the infusion. The etiology is thought to be multifactorial secondary to a decreased platelet dose and platelet activation from the manufacturing process.

A Cochrane database meta-analysis evaluating five clinical trials demonstrated an overall increase in the mean number of platelet transfusions for patients who received pathogen-reduced platelets compared to those who received untreated platelets. In the Cochrane analysis, the Kerkhoffs trial was deemed the highest quality data evaluating untreated platelets suspended in plasma, untreated platelets suspended in PAS III, and pathogen-reduced platelets in PAS III in hematology-oncology patients.[18] The mean (SD) number of doses was 5 (2) platelets in the pathogen-reduced platelet group compared with 4 (2) in the untreated platelet group.

The meta-analysis also identified a decrease in platelet increments for pathogen-reduced platelets, compared to untreated platelets, based on the most statistically significant two studies evaluating the platelet transfusion interval in haematology-oncology patients. The SPRINT trial enrolling thrombocytopenic patients showed a mean (SD) transfusion interval of 1.9 (0.99) days for pathogen reduced PAS apheresis platelets and 2.3 (1.08) days for untreated PAS apheresis platelets. A second study evaluating hematology-oncology patients showed a mean (SD) transfusion interval of 2.03 (0.79) days for pathogen-reduced buffy coat and apheresis platelets in platelet additive solution and 2.49 (0.82) days for untreated buffy coat and apheresis plasma suspended platelets.[29] Overall, the decreased platelet increments are thought be multifactorial from decreased platelets per transfused unit and increased activation markers leading to decreased *in vivo* circulation.[30]

The Cochrane meta-analysis found that the lower platelet increments in patients following transfusion could be overcome with additional platelet transfusions. The additional transfusion did not result in an increase of patient HLA alloimmunization. Thus, possible decreased platelet increments are solely due to non-immune platelet refractoriness and not HLA alloimmunization induced platelet refractoriness. A lower-than-expected platelet increment is resolved with the transfusion of an additional platelet unit. The increased donor exposures through larger donor pooling and possible increased transfusions did not result in increased HLA alloimmunization.[23]

Amotosalen hypersensitivity and activation from some phototherapy devices

PPPT is contraindicated for patients with a history of hypersensitivity reactions to amotosalen or other psoralen products. A supplementary contraindication applies for neonates treated with phototherapy devices that emit a peak energy wavelength of less than 425 nm or a lower bound of the emission bandwidth of less than 375 nm, due to the potential for erythema resulting from the interaction between ultraviolet light and amotosalen. Phototherapy devices operating in the above bandwidth can activate the trace amounts of circulating amotosalen. In immunologically developing neonates, there is a risk of patient white blood cells being inactivated and immune suppression. In the Schulz cohort of 11 patients, there were no instances of new rash associated with concomitant use of phototherapy and PPPT transfusion; the phototherapy devices with a peak energy wavelength higher than the label cut-off wavelength recommended.[24]

Paucity of long-term outcomes in neonatal and intrauterine transfusions

Since the approval of INTERCEPT® treated platelets internationally, a number of studies have described the safety of these products in pediatric and pregnant patient cohorts. Amato et al. evaluated 91 pediatric (<18 years old) and neonates (<30 days old) without any indication of harm.[31] Schulz et al. assessed neonatal intensive care unit patients, infants 0-1 year not in the in the neonatal intensive care unit, and children aged 1–18 years. This study also found no harm to these patients.[24] Lasky et al. reviewed 191 neonatal and pediatric patients receiving 1,010 platelet transfusions, of which 68 patients received only INTERCEPT® treated platelets.[27] There were no increases in adverse events compared with untreated platelets, including those that received phototherapy. Short-term safety data have demonstrated safety, but long-term data are currently limited. The benefit and risk should be carefully assessed and balanced before using PPPT, especially in neonates and for intrauterine transfusion for whom the long-term safety data are very limited. PPPT is considered an alternative platelet source in a situation when the benefit outweighs the risk (e.g., in an emerging pathogen crisis).

Additional resources

For more on pathogen-reduced pooled platelets, visit the OrbCon (Ontario Regional Blood Coordinating Network) website to view or download these resources developed by Dr. Jeannie Callum, director of transfusion medicine at Kingston Health Sciences Centre and affiliate scientist at Canadian Blood Services:

- A five-minute educational video: Bug free platelets
- Email to clinicians example
- PowerPoint Presentation: Bug free platelets
- Information sheet for patients, developed by Dr. Callum in partnership with the Kingston Health Sciences Centre Cancer Centre: Pathogen reduced platelets - What people getting platelet transfusions need to

know

Suggested citation

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