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BACKGROUND

Whole blood donations are separated into specific cellular (red blood cells and platelets) and plasma components. Transfusing the appropriate blood component to effectively provide for the clinical needs of patients optimizes use of donated blood.

This chapter describes the manufacturing process for the most commonly prepared blood components:

- Red blood cells (RBC)
- Platelets: pooled and apheresis
- Frozen plasma (FP)
- Apheresis fresh frozen plasma (AFFP)
- Cryosupernatant plasma (CSP)
- Cryoprecipitate

Brief descriptions of the indications, contraindications, storage and transportation requirements, dose, administration and available alternatives are included in the sections below. Further information may be found in other chapters of this *Guide* as indicated within the different sections.

Canadian Blood Services also publishes a *Circular of Information* to provide an extension of the component label and information regarding component composition, packaging, storage and handling, indications, warnings and precautions, adverse events, dose, and administration. The *Circular* conforms to the applicable regulations issued by the Health Products and Food Branch, Health Canada.

COLLECTION OF BLOOD PRODUCTS

At Canadian Blood Services, whole blood is collected from donors into a collection pack in which multiple bags are connected, allowing blood and components to be transferred between bags aseptically (closed system) during manufacturing. The collection packs include two different configurations:

- The buffy coat collection set (also referred to as B1) is used in the production of RBC, plasma, and platelet components.
- The whole blood filtration set (also referred to as B2) is used in the production of RBC and plasma components (including cryoprecipitate).

Figure 1 highlights the main steps of both manufacturing processes. Both collection sets contain a citrate-phosphate-dextrose (CPD) anticoagulant in the collection bag.

Apheresis technology instead of whole blood collection may also be used for collection of some blood components, including plasma and platelets. This collection procedure utilizes an automated in-line process in which whole blood from the donor enters a collection chamber where centrifugation separates the plasma from cellular blood constituents such as red blood cells and white blood cells. Information about the anticoagulants used can be found in the *Circular of Information* for each component type and in Table 1. Depending on the process, either plasma or platelets suspended in plasma are collected into a bag while the remaining constituents of the blood are returned to the donor.

https://professionaleducation.blood.ca/en/transfusion/clinical-guide/blood-components
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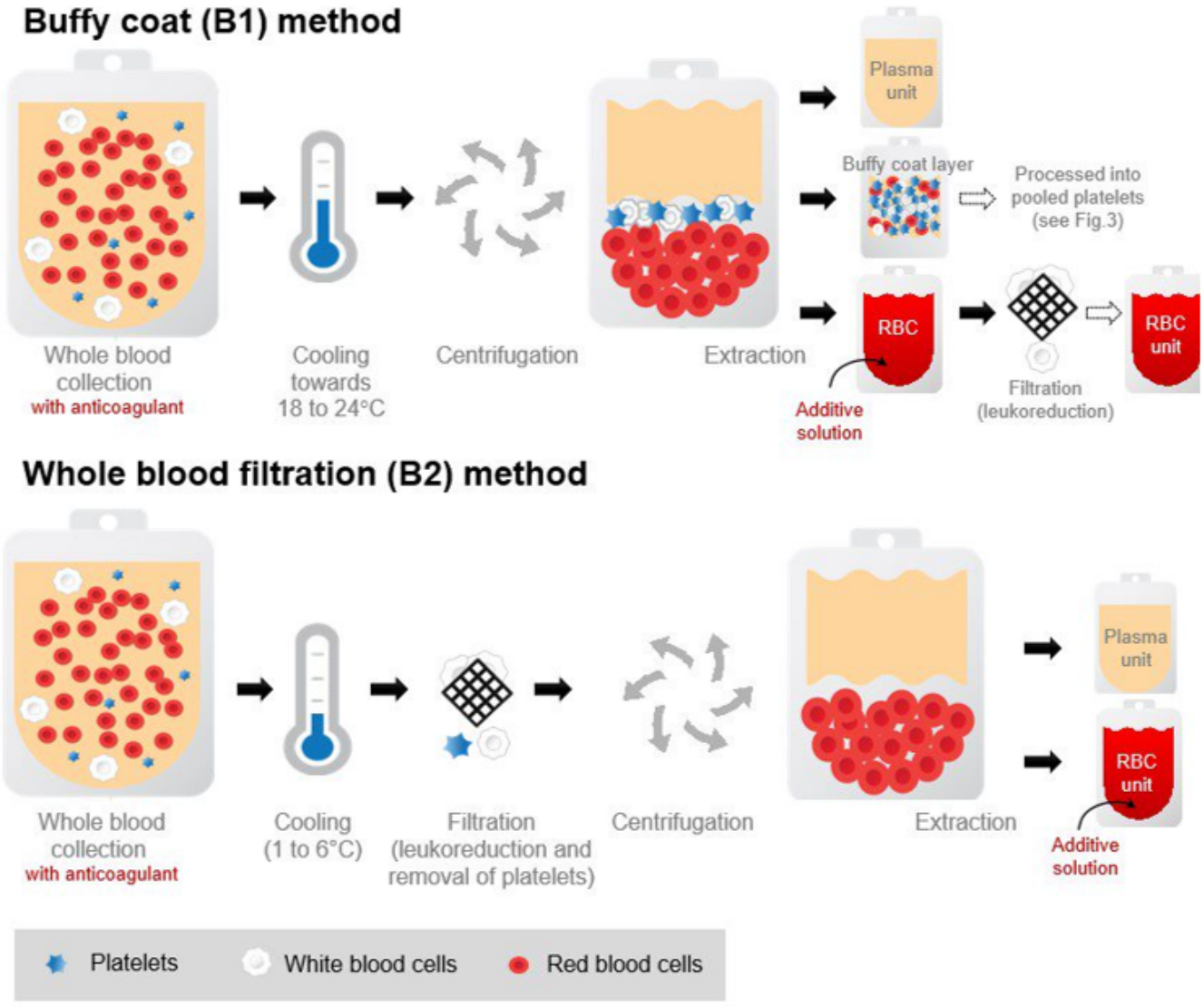

Figure 1. The manufacturing processes used at Canadian Blood Services to produce blood components from whole blood.

RED BLOOD CELLS

Component manufacturing and description

Whole blood collected in CPD anticoagulant is processed by either the B1 or B2 method (Figure 1). In the B1 method, whole blood is centrifuged to separate the red blood cells from the platelets and plasma. The red blood cells are then leukoreduced (LR) by filtration. In the B2 method, the whole blood is first filtered to remove platelets and leukocytes (LR), then centrifuged to separate the red blood cells from the plasma. For both B1 and B2 methods, the red blood cells are then mixed with an additive solution, saline-adenine-glucose-mannitol

(SAGM) and labelled as a red blood cell unit.

All red blood cells prepared by Canadian Blood Services have undergone leukoreduction (LR). The average volume of a red blood cell unit issued by Canadian Blood Services is 293 (± 26) ml, typically contains 56 (± 7) g of hemoglobin with a hematocrit of approximately 0.68 ± 0.03 L/L, and has an average residual leukocyte count of 0.18 x 10^6. These parameters are also described and updated in the *Circular of Information*. Further modifications of red blood cell components such as washing, deglycerolizing and irradiation are covered in Chapter 15 of this *Guide.*

Each donation is tested for various antigens and for a number of infectious diseases outlined in Chapter 6. In addition, all donor red blood cells undergo ABO and Rh D typing and are labelled accordingly (Figure 2). Kell typing is performed on every donor twice and, when negative, this result is printed on the label. A proportion of donors are also phenotyped for additional red cell antigens corresponding to common clinically significant antibodies (C,c,E,e,Jka, Jkb, Fya, Fyb, S,s).Negative results for any of these antigens appear on the label. The complete set of results, including positive and negative antigen tests, appears in the bar code label.

Figure 2: Canadian Blood Services label for a red blood cell unit. Available on blood.ca.

Indications

The primary purpose for a red blood cell transfusion is to increase the oxygen-carrying capacity of the blood. Therefore, red blood cell transfusion is indicated in patients with anemia who have evidence of impaired oxygen delivery. For example, symptomatic acute blood loss, chronic anemia and cardiopulmonary compromise, or disease or medication effects associated with bone marrow suppression may be triggers for red blood cell transfusion. In patients with acute blood loss, volume replacement is often required and, depending on clinical circumstances, plasma and platelets may also be transfused. See Chapter 11 of this *Guide* for details on massive hemorrhage and emergency transfusion.

Effective oxygen delivery depends not only on the hemoglobin level, but also on the cardiovascular condition of the individual, and the associated ability to compensate for decreased hemoglobin concentration. Patients without cardiopulmonary compromise, therefore, will typically tolerate lower hemoglobin levels than patients with limited cardiopulmonary reserve. Similarly, the normal hemoglobin levels of infants and children vary from those seen in adults and transfusion triggers as well as usual blood component dose will also vary according to age. See Chapter 13 of this *Guide* for details on neonatal and pediatric transfusion. Finally, patients who develop anemia slowly develop compensatory mechanisms to allow them to tolerate lower hemoglobin values than patients who become acutely anemic.

The decision to transfuse anemic patients should be based on an individual case assessment. There is no uniformly accepted hemoglobin value below which transfusion should occur for every patient, in every scenario. However, many studies and guidelines support the use of a restrictive transfusion strategy, including in the intensive-care unit (ICU) setting and with postoperative anemia.[1]

Red blood cells are not given for volume replacement or for any reason other than correction of acute or chronic anemia and should be given only after non-transfusion alternatives have been either assessed and excluded or do not adequately manage anemia. The decision to transfuse should not be based on a single hemoglobin or hematocrit value as a trigger without considering all relevant physiologic and surgical factors affecting oxygenation and clinical status in that patient. Cardiovascular status along with other co-morbid conditions, the acuity and severity of the anemia, and the presence or risk for ongoing blood loss are also considered in determining the need for correction of anemia with transfusion. See the Choosing Wisely Canada website for more information about transfusion guidelines.[2]

Dose and administration

One unit of red blood cells (293 (± 26) ml) usually increases the hemoglobin concentration by approximately 10 g/l in an average size (70 kg), non-bleeding adult. For pediatric or neonatal patients, as well as for adult patients who cannot tolerate a transfusion rate that would allow for infusion of the total volume within four hours, small volume or “split” units may be provided by some hospital transfusion services.

Chapter 8 and Chapter 9 of this *Guide* provide detailed information on pre-transfusion testing and administration, respectively. Chapter 13 of this *Guide* is also recommended for guidelines on neonatal and pediatric transfusion.

If transfusion of the red blood cell unit will not be initiated promptly after removal from the temperature-controlled blood component refrigerator or storage/transportation device, it should be returned to inventory immediately to prevent waste. An unused RBC unit may be returned only if the bag is intact, passes a visual inspection and has either been maintained at an acceptable temperature (see Storage and transportation), or

has not been out of a temperature controlled environment for more than 60 minutes (See CSTM Standard 5.8.7.1 for more information).[3]

Storage and transportation

Proper storage and transportation of blood components are critical for safe transfusion. As a biological product, blood carries risk of bacterial contamination if stored improperly. Improper storage may also affect blood component efficacy.

The shelf life of a red blood cell unit issued by Canadian Blood Services is 42 days from collection. Manipulation of the unit, including washing or irradiation, shortens the shelf life. The expiry date is documented on the label of each unit. If the red blood cell unit is opened without the use of a sterile connection device, the shelf life is limited to 24 hours if stored at 1–6°C (or the original expiry date, whichever is sooner), or to 4 hours if stored above 6°C. Units selected for irradiation at Canadian Blood Services must be less than or equal to 14 days old after collection and following irradiation, irradiated cells must be transfused as soon as possible, but not later than 14 days after irradiation.[4-6]

Red blood cell components must be stored at 1–6°C in a temperature-controlled storage device with an alarm system, air-circulating fan and continuous monitoring device. Records must be kept during storage and transportation that maintain the chain of traceability of blood components from their source to final disposition, and to ensure that appropriate conditions were present throughout this time frame. Chapter 15 provides additional information on washing and irradiation.

Maintaining proper storage temperature during transportation is essential. Transportation time for red blood cells should not exceed 27 hours, using shipping containers and standardized packing procedures that have been validated to maintain an environmental temperature of 1–6°C. For transit times of 24 hours or less, a transport system validated to maintain an environmental temperature of 1–10°C is allowable. Visual inspection of each blood component to be shipped must be performed and documented at the time of shipping and receiving. Some hospitals and regions use temperature-monitoring devices in one or more shipping containers with each shipment of blood and blood components to ensure the correct temperature during transportation.

When red blood cell units accompany a patient who is transferred from one facility to another, traceability of the RBC must be maintained. Accordingly, the issuing hospital transfusion service is responsible for notifying the receiving hospital transfusion service, which is then responsible for the final disposition documentation including whether the RBC was transfused to a patient or was discarded.

Further details about the red blood cell units manufactured by Canadian Blood Services can be found in the *Circular of Information for the Use of Human Blood Components, Red Blood Cells, Leukocytes Reduced.*

Available alternatives

Depending on the underlying cause of anemia, alternative treatments that may be considered include oral iron, intravenous iron, vitamin B12, folic acid, and/or erythropoietin stimulating agents. Monitoring the patient while treating the underlying condition(s) contributing to anemia may be an alternative to transfusion for some patients.[2]

PLATELETS

Component manufacturing and description

At Canadian Blood Services, there are two types of platelet preparations: pooled platelets and apheresis platelets.

Pooled platelets are prepared from whole blood collected into a buffy coat collection set (B1 method) with CPD anticoagulant (Figure 1). The whole blood donations are cooled to room temperature after collection. After transportation to the production site, the blood components are separated by centrifugation. The top layer, containing the plasma, and the bottom layer, containing the red blood cells, are extracted. The buffy coat layer between the red blood cells and plasma contains platelets and white blood cells. The buffy coat layers from four donations of the same ABO blood group, along with plasma from one of the same four donations (a male donor), are pooled together and processed further, including LR by filtration, in order to produce one pooled platelet unit or dose (Figure 2). The pool is labeled as Rh negative only when all the donor units within the pooled component are Rh negative. Pooled platelet units are produced within 28 hours of collection and have a unique pool number identifier. Pooled platelets have an average volume of 342 (± 15) ml and a typical platelet count of 298 (± 68) x 10^9 per unit. The shelf life is seven days from the time of collection. The typical unit of pooled platelets has an average residual leukocyte count of 0.09 x 10^6 and may also contain trace amounts of red blood cells.

Apheresis platelets are collected and prepared by an automated in-line process using apheresis machines that separate and extract platelets (suspended in the donor's plasma) from other cellular whole blood components by centrifugation. A typical unit of apheresis platelets issued by Canadian Blood Services contains 370 (± 48) x 10^9 platelets, with a mean residual leukocyte count of 0.067 x 10^6 and an average volume of 242 (± 8) ml.

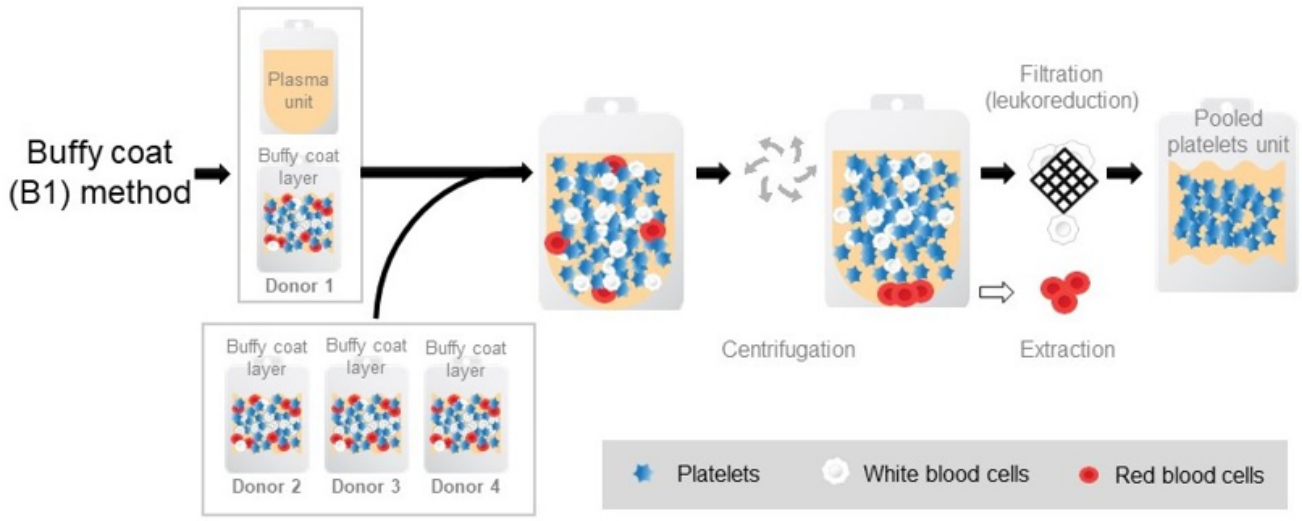

Figure 2. Pooled Platelets manufacturing at Canadian Blood Services.

Indications

The transfusion of platelets is indicated in the treatment of patients with bleeding due to severely decreased or dysfunctional platelets. Platelet transfusion may also be useful if given prophylactically to patients with rapidly

falling or low platelet counts secondary to bone marrow disorders or chemotherapy. Platelet transfusions are not recommended for patients with rapid platelet destruction (e.g., immune thrombocytopenic purpura (ITP), heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP)) except in the setting of clinically significant and/or life-threatening bleeding.[7]

Indications are similar for both pooled platelets and apheresis platelets. Apheresis platelets may be selected based on similar human leukocyte antigen (HLA) typing to the recipient's when a recipient fails to respond to platelet transfusion because of demonstrated anti-HLA antibodies (alloimmune refractoriness). See Chapter 18 of this *Guide* for details of treatment and testing for platelet-refractory patients.

Dose and administration

While ABO-identical platelets may be preferred for transfusion of some patients, ABO compatible platelets are often used. See Chapter 9 and Chapter 18 of this *Guide* for information on ABO compatibility, dose and administration of platelet components.

Transfusion of apheresis platelets should result in increments similar to those achieved by transfusion of pooled platelets. Each dose of platelets should increase the patient's platelet count at 1 hour by at least 15-25 x 10^9/l in a standard sized-adult.[8]

In practice, the post-transfusion platelet count often does not rise to the expected level. Sepsis, alloimmunization, fever, ITP, or disseminated intravascular coagulation (DIC) may contribute to a suboptimal response. See Chapter 18 of this *Guide* for more information.

Storage and transportation

Platelet components must be stored at 20–24°C under continuous agitation. If the agitator is not a closed platelet incubator, the ambient temperature must be recorded manually using a calibrated thermometer every four hours or through use of a constant room temperature monitoring device.

Both pooled platelets and apheresis platelets have a shelf life of seven days from the date of collection. Once opened, the unit expiry time is four hours from the time of opening unless aliquots are prepared using a sterile connection device. Aliquots obtained using such a device retain the original seven-day expiry date and must contain a minimum residual volume that is dependent on the collection pack. Canadian Blood Services collects apheresis platelets using Terumo Trima collection packs, which have a minimum volume of 100 ml. The collection and expiry dates indicated on the platelet unit must be copied to the label of each aliquot pack made from the original unit.

Further details on the platelet components manufactured by Canadian Blood Services can be found in the *Circular of Information for the Use of Human Blood Components, Platelets*, and Chapter 18 of this *Guide*.

Available alternatives

Apheresis platelets may be substituted for pooled platelets if supply and demand allow.

There are no known alternatives to platelet concentrates.

PLASMA PRODUCTS

Component manufacturing and description

Canadian Blood Services manufactures and distributes the following main types of plasma components:

- Frozen plasma CPD (FP)
- Apheresis fresh frozen plasma (AFFP)
- Cryosupernatant plasma CPD (CSP)
- Cryoprecipitate (see cryoprecipitate section later in this chapter)

Canadian Blood Services also distributes:

- Solvent detergent treated (SD) plasma. Produced by Octapharma, this product is for specific patients who have conditions requiring use of this product (discussed later in this chapter)

Blood donors are screened for the presence of antibodies to red cell antigens. If a clinically significant antibody is identified, the plasma is discarded.

Frozen plasma CPD (FP) is prepared from whole blood collected in CPD anticoagulant that is red blood cell-reduced by centrifugation. FP produced by the B1 method is both leukoreduced and platelet-reduced by centrifugation but not leukoreduced by filtration. FP produced by the B2 method is both platelet-reduced and leukoreduced by filtration (Figure 1). The extracted plasma is frozen within 24 hours of collection and labelled as a frozen plasma CPD unit. The processing steps inherently reduce the number of leukocytes to a residual leukocyte level that averages $< 5 \times 10^6$ per unit, although individual unit leukocyte level can be highly variable. FP components are not labeled as LR.

For pediatric patients requiring small volume transfusions, Canadian Blood Services offers divided plasma units (FP-Divided) which contain 125–150 ml of plasma. FP-Divided is blood group AB, unless otherwise requested.

Apheresis fresh frozen plasma (AFFP) is collected by an automated in-line process using apheresis machines that separate and extract plasma from cellular whole blood components by centrifugation. Plasma collected by apheresis is frozen within eight hours of collection and labelled as an AFFP unit.

The average volume of FP and AFFP components issued by Canadian Blood Services and their coagulation factors content are described in Table 1. Coagulation factors V and VIII are labile coagulation factors and are not stable in plasma stored for prolonged periods at 1–6˚C; therefore, plasma is stored in the frozen state at -18˚C or lower. AFFP contains approximately 87% of the factor VIII present at the time of collection, and according to Canadian standards must contain at least 0.70 IU/ml of factor VIII in at least 75% of the units tested. FP contains factor VIII levels that are approximately 70–75% of the levels present at the time of collection, and according to Canadian standards must contain at least 0.52 IU/ml of factor VIII, in at least 75% of the units tested. The levels of factor V, as well as the levels of other coagulation factors, are not significantly decreased from baseline in plasma frozen within 24 hours of collection.

Cryosupernatant plasma CPD (CSP) is prepared from slowly thawed FP that is centrifuged to separate the plasma from the insoluble cryoprecipitate. The insoluble cryoprecipitate is removed and refrozen and the remaining plasma is also refrozen and labelled as cryosupernatant plasma CPD.

Canadian Blood Services also distributes Octaplasma™ for use in a limited number of patients who meet specific criteria. This is a solvent detergent (SD) treated, pooled fresh frozen plasma component produced by Octapharma. Octaplasma™ is filtered to remove cells and debris, which may help reduce adverse events linked

to residual blood cells, and the pooling process dilutes and neutralizes allergens and antibodies, theoretically reducing the risk of transfusion-related acute lung injury (TRALI). The SD treatment destroys enveloped viruses and the manufacturing process reduces (although does not entirely eliminate) the risk of infection by non-enveloped viruses and prions.

Convalescent plasma is plasma that is collected from people who have recovered from an infection and their plasma contains neutralizing antibodies against the causative pathogen. Convalescent plasma has been used as an experimental therapy to treat SARS[9], H1N1[10], Ebola[11, 12] and, most recently, COVID-19.[13-15]

Prior to the COVID-19 pandemic, there were no large-scale randomized trials that demonstrated efficacy of convalescent plasma. Systematic reviews of trials that used convalescent plasma or hyperimmune products to treat viral pneumonias concluded that convalescent plasma may be associated with efficacy and lack of harm (very low quality evidence), and that well-designed clinical trials are needed.[16, 17] During the year 2020, hundreds of studies were initiated world-wide to determine safety and efficacy of convalescent plasma in treating COVID-19. Canadian Blood Services, along with Héma-Québec have been supporting large-scale randomized control trials in Canada by collecting, testing and providing COVID-19 convalescent plasma for use in Health Canada approved clinical trials. Convalescent plasma is collected using apheresis from donors who meet eligibility criteria for routine apheresis plasma collection; in addition, the donors must be previously confirmed positive for COVID-19 by a laboratory test, fully recovered from the virus and symptom free for at least 28 days.

Table 1. Description of plasma components distributed by Canadian Blood Services

Type	Description
Frozen Plasma CPD (FP)	Approximately 283 ml of plasma separated from an individual unit of whole blood collected in CPD anticoagulant and placed in a freezer at ≤-18˚C within 24 hours after collection; contains all coagulation factors but has slightly reduced amounts of clotting Factors V and VIII. On average, FP contains 0.87 IU of Factor VIII per ml.
Apheresis Fresh Frozen Plasma (AFFP)	Plasma collected by apheresis and frozen within eight hours of collection; contains both labile clotting Factors V and VIII, plus non-labile coagulation factors. Sodium citrate anticoagulated AFFP units have an average volume of 494 ml while ACD-A (acid citrate dextrose – Solution A) anticoagulated AFFP units have an average volume of 249 ml. AFFP units contain an average of 1.29 IU of Factor VIII per ml
Cryosupernatant Plasma CPD (CSP)	Approximately 273 ml of plasma separated from an individual unit of whole blood prepared following cryoprecipitate manufacturing; contains all coagulation factors but has reduced levels of the high molecular weight Von Willebrand factor (vWF) multimers and fibrinogen.
Solvent Detergent (SD) plasma	Plasma pooled from many donors, treated with processing steps (solvent detergent, immune neutralisation, sterile filtration) to remove or inactivate pathogens, cells, allergens and antibodies. Each unit is 200 ml of cell-free plasma that contains 9.0–14.0 g of human plasma proteins (45–70 mg/ml). A minimum of 0.5 IU per ml is obtained for all clotting factors.
Convalescent Plasma (CCP)†	Plasma collected from people who have recovered from an infection and that contains neutralizing antibodies against the causative pathogen. Content description for AFFP above applies; in addition, plasma must demonstrate a pre-specified neutralizing antibody titre.

FP, AFFP and CSP are manufactured and distributed by Canadian Blood Services. SD plasma (Octaplasma™) is produced by Octapharma and distributed by Canadian Blood Services for specific indications. See component

monograph for more details.

†CCP is currently manufactured for ongoing clinical trials and is not yet part of the Canadian Blood Service license for distribution outside of these clinical trials.

Indications

Since AFFP is no longer used to treat patients with isolated factor VIII or Von Willebrand factor deficiencies and studies have shown that the levels of factor VIII in FP are only slightly lower than those in AFFP, in most clinical situations where these components are indicated (Table 2), FP and AFFP may be used interchangeably.

The use of AFFP/FP is limited almost exclusively to the treatment or prevention of clinically significant bleeding due to a deficiency of one or more plasma coagulation factors for which more appropriate or specific alternative therapy is not available. Such situations potentially include the treatment of:

- Bleeding patients or patients undergoing invasive procedures who require replacement of multiple coagulation factors (such as patients with severe liver disease or disseminated intravascular coagulation (DIC))
- Patients with massive hemorrhage with clinically significant coagulation abnormalities
- Patients on warfarin anticoagulation who are bleeding or need to undergo an invasive procedure before vitamin K can reverse the warfarin effect and for whom prothrombin complex concentrates are not indicated, or not available
- Patients requiring treatment of TTP and adult hemolytic uremic syndrome (HUS) by plasma exchange or
- Other conditions treated by therapeutic plasma exchange where the exchange fluid must include coagulation factors. See Chapter 14 of this *Guide.*

AFFP or FP may also be used in the preparation of reconstituted whole blood for exchange transfusion in neonates. See Chapter 13 of this *Guide* for more information about neonatal and pediatric plasma transfusion.

Cryosupernatant plasma CPD (CSP) is used in the treatment of TTP and adult hemolytic uremic syndrome (HUS) by plasma exchange, or may be used in treatment of multifactor deficiency, particularly when fibrinogen replacement is not required. For example, CSP may also be used for treatment of patients on warfarin anticoagulation who are bleeding or need to undergo an invasive procedure before vitamin K can reverse the warfarin effect and for whom prothrombin complex concentrates are not indicated, or not available. AFFP or FP may also be used in these situations and have equivalent efficacy. Frozen plasma and CSP have also been shown to have the same efficacy in the treatment of patients with TTP.[18, 19]

Octaplasma™ is licensed and approved for use in Canada for a number of indications where plasma might otherwise be used. However, the supply is limited, and only patients with high volume plasma transfusions who meet criteria identified by the National Advisory Group[20] on Blood and Blood Products may be treated with SD plasma, including patients with:

- thrombotic thrombocytopenic purpura (TTP)
- hemolytic uremic syndrome (HUS) with associated factor H deficiency or
- clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII)

who also:

- have experienced an allergic reaction to a frozen plasma component (e.g., AFFP, FP) or
- have a pre-existing lung disorder or
- need a frozen plasma component but a blood group compatible component is not available in a timely manner.

Table 2. Indications for plasma component transfusion by condition/clinical circumstance

Condition/Clinical Circumstance	Frozen Plasma CPD (FP)	Apheresis Fresh Frozen Plasma (FFPA)	Cryosupernatant Plasma CPD (CSP)	Solvent Detergent (SD) Plasma
Reversal of warfarin therapy when prothrombin complex concentrates and/or vitamin K is contra-indicated or unavailable	X	X	X	
Correction of microvascular bleeding when laboratory testing demonstrates coagulopathy	X	X		
Liver disease	X	X		
Massive transfusion	X	X		
Exchange transfusion in neonates	X	X		
TTP or adult HUS plasma exchange therapy	X	X	X	
Patients with selected coagulation factor deficiency or rare plasma protein deficiencies when specific alternative therapy is not available	X	X		
Patients who meet the qualifying criteria for SD plasma (see above)				X

Guidelines for reversal of oral anticoagulant therapy using plasma or prothrombin complex concentrates (PCC) are available from the National Advisory Committee on Blood and Blood products.[21] See also Chapter 17 of this *Guide* and/or the relevant Canadian Blood Services *Circular of Information for the Use of Human Blood Components, Plasma Components,* for further information.

Contraindications

Plasma transfusion is **not** indicated for volume replacement alone, or for a single coagulation factor deficiency if specific recombinant products or plasma-derived virally inactivated products are available. Plasma transfusion is generally not indicated or effective in reversal of an International Normalized Ratio (INR) below 1.8.[22]

Hypovolemia without coagulation factor deficiencies should be treated with other plasma volume expanders such as 0.9% sodium chloride, Ringer's lactate solution or albumin. See Chapter 3 of this *Guide* for more details on albumin and therapeutic alternatives to albumin.

Do not use plasma when coagulopathy can be more appropriately corrected with specific therapy such as vitamin K, prothrombin complex concentrates (PCCs), cryoprecipitate, or specific coagulation factor replacement. See Chapter 5 of this *Guide* for information about coagulation factors available in Canada and their use.

Do not use CSP for conditions that require fibrinogen, factor VIII or Von Willebrand factor replacement.

Dose and administration

Chapter 9 and Chapter 13 of this *Guide* are recommended for detailed information on blood administration and on neonatal and pediatric transfusion, respectively.

The volume transfused depends on the clinical situation and recipient size, and when possible should be guided by serial laboratory assays of coagulation function. In general, the dose to achieve a minimum of 30% of plasma clotting factor concentration is attained with administration of 10–15 ml/kg of body weight, except for treatment of warfarin reversal in which 5–8 ml/kg body weight will usually suffice (and only in the rare circumstance where PCCs are contraindicated or unavailable).

Plasma components must be ABO compatible with the recipient but are not necessarily required to be group specific. In most clinical circumstances, the plasma component should not contain ABO antibodies that may be incompatible with the ABO antigens on the patient's red blood cells. If there is no ABO group available for the recipient, a typing will be required to determine compatibility. Alternatively, group AB plasma can be used, although for initial management of massive hemorrhage, many North American trauma centres use group A plasma over group AB plasma in their massive hemorrhage protocols; however, this is not yet standard practice across Canada".

Thawing of FP, AFFP and CSP may take 12–30 minutes depending on the component volume, thawing method and equipment used by the hospital transfusion service. SD plasma (Octaplasma™) should be thawed in the outer wrapper in a circulating water bath (30–37°C) for 30 to 60 minutes or in a dry tempering system according to manufacturer instructions; detailed device-specific recommendations are available from Octapharma.

Upon completion of thawing, transfuse immediately or store plasma components in an alarmed, continuously temperature-monitored refrigerator at 1–6°C. Once thawed, plasma components cannot be refrozen; some institutions have a thawed plasma bank. FP, CSP, and AFFP anticoagulated with ACD-A can be stored up to five days; however, AFFP anticoagulated with sodium citrate is collected in an open system and can be stored for only 24 hours (at 1–6°C) after thawing.

If transfusion of the plasma unit will not be initiated promptly after removal from the temperature-controlled blood component refrigerator or storage/transportation device, it should be returned immediately to inventory to prevent waste. Blood components may be returned only if the bag is intact, passes a visual inspection and has maintained an acceptable temperature (See CSTM Standard 5.8.7.1 for more information).[3] Frozen plasma, once thawed cannot be re-frozen but may be used for other patients requiring plasma until the post-thaw expiry is reached.

Storage and transportation

Frozen plasma components must be stored frozen at -18°C or colder in a controlled, temperature-monitored freezer for a maximum of 12 months (FP, AFFP, CSP) or four years (Octaplasma™). Components must not be out

of a temperature-controlled blood storage freezer for longer than 30 minutes.

Available alternatives

FP and AFFP may be used interchangeably depending on indication, supply and demand.

SD plasma (Octaplasma™) is available for specific indications as described above.

Vitamin K should be used for warfarin reversal when the patient is not bleeding and does not require an invasive procedure. Patients requiring rapid reversal of warfarin due to bleeding, bleeding risk or an urgent invasive procedure may benefit from use of a PCC along with Vitamin K. Practical guidance on warfarin reversal can be found on Treat the Bleed, an evidence-based, online resource for front-line physicians.

Specific plasma protein concentrates are available and are described in Chapter 5 and Chapter 17 of this *Guide*.

CRYOPRECIPITATE

Component manufacturing and description

Canadian Blood Services prepares cryoprecipitate from slowly thawed FP that is centrifuged to separate the insoluble cryoprecipitate from the plasma. The plasma is removed, and the insoluble component is refrozen and labelled as cryoprecipitate. Typically, one unit of cryoprecipitate (10 ± 2 ml) is obtained from one unit of FP. Each unit of cryoprecipitate contains a mean of 285 (± 88) mg of fibrinogen.

Indications

Over the last several years, a number of factors have changed the clinical indications for the use of cryoprecipitate. These factors include a better understanding of the coagulation system, more attention to the non-factor VIII constituents within cryoprecipitate, concern about viral inactivation, and the development of alternative components.

The current primary uses of cryoprecipitate are for fibrinogen replacement in acquired hypofibrinogenemia or as empiric therapy in a bleeding patient.[23, 24] Although either cryoprecipitate or fibrinogen concentrate can be utilized for fibrinogen replacement therapy, the concentrate has the advantage of being pathogen-reduced and available in a freeze-dried, powdered form, which makes it easier to reconstitute and administer than cryoprecipitate, which must remain frozen until use. For these reasons, fibrinogen concentrate is increasingly used in Canada for treatment of acquired hypofibrinogenemia.[23, 24] Production of cryoprecipitate from a donor unit precludes platelet production; thus, in the event of a platelet shortage, optimizing platelet production may lead to decreased cryoprecipitate production and recommendations for use of fibrinogen as an alternative. See Chapter 5 of this *Guide*.

Generally, a plasma fibrinogen level of less than 1.0 g/l, as might occur in DIC or fibrinogenolysis, provides an objective basis for fibrinogen replacement. Certain populations have a higher threshold (e.g., fibrinogen <2.0 g/L in massively bleeding obstetrical patients, and fibrinogen <1.5 g/L for other massively hemorrhaging patients or patients with acute promyelocytic leukemia). [3, 24-26]

The historical use of cryoprecipitate as a factor VIII and VWF concentrate for hemophilia and Von Willebrand disease has now been replaced through treatment regimens that utilize recombinant clotting factor

concentrates. Cryoprecipitate was, until recently, widely accepted as one of the components used to treat bleeding due to congenital or acquired hypofibrinogenemia with multiple factor deficiencies (e.g. DIC, post-thrombolytics, massive transfusion or liver disease). These conditions are complicated and fibrinogen replacement is often only one part of the spectrum of clinical management of such patients. A recent study confirms the efficacy of fibrinogen concentrate in treating acquired hypofibrinogenemia consequently many hospitals have shifted to use of concentrates rather than cryoprecipitate.[23]

Contraindications

Usually, cryoprecipitate **is not indicated** unless results of laboratory studies indicate a fibrinogen concentration of 1.0 g/l or less or in the setting of massive hemorrhage with coagulopathy. Specific factor and/or recombinant concentrates are preferred, when available, because of the reduced risk of transfusion-transmissible diseases.

Cryoprecipitate should not be used to make fibrin glue. Virally inactivated commercial products should be used for this purpose.

Cryoprecipitate is not recommended in the treatment of hemophilia A, or in most cases (see below) in the treatment of Von Willebrand disease. Fibrinogen concentrates may be preferred in treatment of hypofibrinogenemia.

Dose and administration

Group-specific cryoprecipitate is not necessary outside of the pediatric setting and should be considered according to local policy for pediatric recipients. Chapter 9 and Chapter 13 of this *Guide* are recommended for detailed information on blood administration and on neonatal and pediatric transfusion, respectively.

One unit of cryoprecipitate contains approximately 285 mg of fibrinogen. The amount of cryoprecipitate required for transfusion will depend on the severity and nature of the bleeding condition.

The amount of cryoprecipitate needed to raise the fibrinogen concentration of plasma can be calculated (see Figure 4). However, it is common practice to use a generic dose of 1–2 cryoprecipitate units per 10 kg body weight as a single dose, with additional doses as required to maintain the fibrinogen level for the clinical scenario. An order of 10 units of cryoprecipitate for an average-sized adult patient is a typical dose.

Step 1	Weight of the patient (kg) x 70 ml/kg = blood volume in ml.
Step 2	Blood volume in ml x (1.0 – patient hematocrit) = plasma volume in ml.
Step 3	Desired fibrinogen – actual fibrinogen x plasma volume (ml) = mg fibrinogen required.
Step 4	mg fibrinogen required/285 mg per cryoprecipitate unit = units of cryoprecipitate required.

Figure 4. Steps to calculate the amount of cryoprecipitate needed to raise the fibrinogen concentration of plasma.

Cryoprecipitate is often pooled by hospital transfusion medicine service personnel or may be given as individual units sequentially. Small quantities of normal saline are introduced to rinse each bag in the pooling process. Pooled cryoprecipitate may have a single pool number and the label will indicate the number of units in the pool. This number and the number of units in the pool must be documented. If no pool number exists, each donor unit number must be documented on the medical record. If the cryoprecipitate is pooled, all units will

have been opened and must be used within four hours.

Cryoprecipitate may be administered through a blood administration set with a standard blood filter or as a filtered bolus injection by trained personnel. Infusion should be as rapid as can be tolerated by the patient or as specified by the ordering physician.

Storage and transportation

Cryoprecipitate must be stored frozen at -18°C or colder in a temperature controlled, monitored freezer for a maximum of 12 months. Components must not be out of the temperature-controlled blood storage freezer for longer than 30 minutes and cannot be refrozen. If the transfusion will not be initiated promptly after removal from the temperature controlled blood component storage device, the component should be returned immediately to prevent deterioration and waste (CSTM Standard 5.8.7.1).[3] Once thawed, cryoprecipitate should be stored at 20-24°C, and transfused within 4 hours.

More information about cryoprecipitate can be found in the *Circular of Information for the Use of Human Blood Components, Plasma Components*.

Available alternatives

The primary use of cryoprecipitate is for fibrinogen replacement, or empirically in a bleeding patient or patient with new microvascular bleeding.

See Chapter 5 of this *Guide* for information on coagulation factor concentrates available in Canada and their use. There are fibrinogen concentrates available and these may be used instead of cryoprecipitate for fibrinogen replacement. See also Chapter 17 of this *Guide* for information on treating hemostatic disorders including hemophilia and Von Willebrand disease. Cryoprecipitate does contain fibronectin that has been suggested and used to improve reticuloendothelial function in critically ill patients with sepsis. There is, however, insufficient evidence to recommend its use in this setting.

ADDITIONAL RESOURCES

Manufacturing blood components from whole blood. Download this poster that includes an overview of how blood components are produced from whole blood using the buffy coat (B1) and whole blood (B2) methods.

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the *Clinical Guide to Transfusion* as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to two credits.

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If you have questions about the *Clinical Guide to Transfusion* or suggestions for improvement, please contact us through the Clinical Guide feedback form.

REFERENCES

1. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, Peterson N, Ramsey G, Rao SV, Roback JD, Shander A, Tobian AA. Clinical Practice Guidelines from the Aabb: Red Blood Cell Transfusion Thresholds and Storage. *JAMA* 2016; 316: 2025-35. https://www.ncbi.nlm.nih.gov/pubmed/27732721.
2. Canadian Society for Transfusion Medicine. Transfusion Medicine Recommendations, Choosing Wisely Canada2015. https://choosingwiselycanada.org/transfusion-medicine/ (Last accessed July 24 2017).
3. CSTM Standards Committee. *Cstm Standards for Hospital Transfusion Services*. Published in Ottawa, Canada by Canadian Society for Transfusion Medicine, 2017.
4. Canadian Blood Services. Customer Letter # 2017-29: Important Information Regarding Changes to the Expiry Date of Irradiated Red Blood Cells. 2017. https://blood.ca/sites/default/files/CL_2017-29.pdf.
5. National Advisory Committee on Blood and Blood Products. Recommendations for Use of Irradiated Blood Components in Canada: A Nac and Ccnmt Collaborative Initiative. 2018. https://nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Blood_Components.pdf.
6. European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). The Guide to the Preparation, Use and Quality Assurance of Blood Components, 20th Edition, 2020.
7. Nahirniak S, Slichter SJ, Tanael S, Rebulla P, Pavenski K, Vassallo R, Fung M, Duquesnoy R, Saw CL, Stanworth S, Tinmouth A, Hume H, Ponnampalam A, Moltzan C, Berry B, Shehata N, International Collaboration for Transfusion Medicine Guidelines. Guidance on Platelet Transfusion for Patients with Hypoproliferative Thrombocytopenia. *Transfus Med Rev* 2015; 29: 3-13. http://www.ncbi.nlm.nih.gov/pubmed/25537844.
8. Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte Reduction and Ultraviolet B Irradiation of Platelets to Prevent Alloimmunization and Refractoriness to Platelet Transfusions. *N Engl J Med* 1997; 337: 1861-9.
9. Cheng Y, Wong R, Soo YOY, Wong WS, Lee CK, Ng MHL, Chan P, Wong KC, Leung CB, Cheng G. Use of Convalescent Plasma Therapy in Sars Patients in Hong Kong. *European Journal of Clinical Microbiology and Infectious Diseases* 2005; 24: 44-6. https://doi.org/10.1007/s10096-004-1271-9.
10. Hung IF, To KK, Lee C-K, Lee K-L, Chan K, Yan W-W, Liu R, Watt C-L, Chan W-M, Lai K-Y, Koo C-K, Buckley T, Chow F-L, Wong K-K, Chan H-S, Ching C-K, Tang BS, Lau CC, Li IW, Liu S-H, Chan K-H, Lin C-K, Yuen K-Y. Convalescent Plasma Treatment Reduced Mortality in Patients with Severe Pandemic Influenza a (H1n1) 2009 Virus Infection. *Clinical Infectious Diseases* 2011; 52: 447-56. https://doi.org/10.1093/cid/ciq106.
11. Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, Baker S, Nicol S, Conton B, Johnson W, Abiri OT, Kargbo O, Kamara P, Goba A, Russell JBW, Gevao SM. Evaluation of Convalescent Whole Blood for Treating Ebola Virus Disease in Freetown, Sierra Leone. *Journal of Infection* 2017; 74: 302-9. https://doi.org/10.1016/j.jinf.2016.11.009.
12. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba NF, Antierens A, Lomas C, Faye O, Sall AA, Fransen K, Buyze J, Ravinetto R, Tiberghien P, Claeys Y, De Crop M, Lynen L, Bah EI, Smith PG, Delamou A, De Weggheleire A, Haba N. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. *New England Journal of Medicine* 2016; 374: 33-42. https://www.nejm.org/doi/full/10.1056/NEJMoa1511812.
13. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou

Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X. Effectiveness of Convalescent Plasma Therapy in Severe Covid-19 Patients. *Proceedings of the National Academy of Sciences* 2020; 117: 9490-6. https://www.pnas.org/content/pnas/117/17/9490.full.pdf.

14. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients with Covid-19 with Convalescent Plasma. *JAMA* 2020; 323: 1582-9. https://doi.org/10.1001/jama.2020.4783.

15. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S. Treatment with Convalescent Plasma for Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest* 2020; 158: e9-e13.

16. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, Makki S, Rooney KD, Group CPS, Nguyen-Van-Tam JS, Beck CR, Mateus ALP, Reuter S, Shin J, Xu X, Pereyaslov D, Papieva I, Tegnell A, Englund H, Elfving Å, Cox R, Mohn KG-I, Jenkins YF. The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-Analysis. *The Journal of Infectious Diseases* 2014; 211: 80-90. https://doi.org/10.1093/infdis/jiu396.

17. Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, Couban R, Bégin P, Guyatt G. Efficacy and Safety of Convalescent Plasma for Severe Covid-19 Based on Evidence in Other Severe Respiratory Viral Infections: A Systematic Review and Meta-Analysis. *Canadian Medical Association Journal* 2020; 192: E745-E55. https://www.cmaj.ca/content/cmaj/192/27/E745.full.pdf.

18. Rock G, Anderson D, Clark W, Leblond P, Palmer D, Sternbach M, Sutton D, Wells G, Group motCA, Nurses motCAoA. Does Cryosupernatant Plasma Improve Outcome in Thrombotic Thrombocytopenic Purpura? No Answer Yet. *Br J Haematol* 2005; 129: 79-86. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2141.2005.05418.x.

19. Zeigler ZR, Shadduck RK, Gryn JF, Rintels PB, George JN, Besa EC, Bodensteiner D, Silver B, Kramer RE. Cryoprecipitate Poor Plasma Does Not Improve Early Response in Primary Adult Thrombotic Thrombocytopenic Purpura (Ttp). *J Clin Apher* 2001; 16: 19-22.

20. National Advisory Committee on Blood and Blood Products. Framework for Appropriate Use and Distribution of Solvent Detergent Treated Plasma in Canada. 2015. http://www.nacblood.ca/resources/guidelines/SD%20Plasma/SD-plasma.pdf.

21. Canadian National Advisory Committee on Blood and Blood Products. Nac's Statement Regarding Appropriateness of Use of Cytomegalovirus (Cmv) Sero Negative Vs Cmv Safe Product. http://www.nacblood.ca/resources/guidelines/CMV.html (Last accessed August 1 2017).

22. Callum JL, Pinkerton PH, Lima A, Lin Y, Karkouti K, Lieberman L, Pendergrast JM, Robitaille N, Tinmouth AT, Webert KE, . *Bloody Easy 4: Blood Transfusions, Blood Alternatives and Transfusion Reactions*. Published in Ontario, Canada by Ontario Regional Blood Coordinating Network, 2016. http://transfusionontario.org/en/download/bloody-easy-4-blood-transfusions-blood-alternatives-and-transfusion-reactions-a-guide-to-transfusion-medicine-fourth-edition/.

23. Callum J, Farkouh ME, Scales DC, Heddle NM, Crowther M, Rao V, Hucke H-P, Carroll J, Grewal D, Brar S, Bussières J, Grocott H, Harle C, Pavenski K, Rochon A, Saha T, Shepherd L, Syed S, Tran D, Wong D, Zeller M, Karkouti K, Group ftFR. Effect of Fibrinogen Concentrate Vs Cryoprecipitate on Blood Component Transfusion after Cardiac Surgery: The Fibres Randomized Clinical Trial. *JAMA* 2019; 322: 1966-76. https://doi.org/10.1001/jama.2019.17312.

24. National Advisory Committee on Blood and Blood Products. Nac Statement on Fibrinogen Concentrate, 2018. https://www.nacblood.ca/resources/guidelines/downloads/NAC_fibrinogen_concentrate_FINAL.pdf.

25. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR. The European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma: Fourth Edition. *Crit Care* 2016; 20: 100. https://www.ncbi.nlm.nih.gov/pubmed/27072503.

26. Stein E, McMahon B, Kwaan H, Altman JK, Frankfurt O, Tallman MS. The Coagulopathy of Acute Promyelocytic Leukaemia Revisited. *Best Pract Res Clin Haematol* 2009; 22: 153-63. https://www.ncbi.nlm.nih.gov/pubmed/19285282.