Review Article

Plasma products for transfusion: an overview

Erin E. Horstman, Christopher A. Tormey

Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Erin E. Horstman, MD. Department of Laboratory Medicine, Yale University School of Medicine, 333 Cedar Street, PO Box 208035, New Haven, CT 06520, USA. Email: erin.horstman@yale.edu.

Abstract: The use of plasma and cryoprecipitated blood components remains a vital part of transfusion therapy for actively hemorrhaging patients, as well as for bleeding prophylaxis for patients at increased risk of bleeding for a variety of reasons. Plasma also continues to be an essential replacement fluid for patients undergoing therapeutic plasma exchange (TPE), among its many other applications. However, over the past 5–10 years, there have been numerous advancements in plasma and cryoprecipitated components, including significant changes to the ways in which these products are collected, processed, modified, and manufactured for human use. Moreover, our understanding of indications and dosing for these products has also evolved, with more readily available evidence-based guidance and laboratory cutoffs. The last decade has also seen a rise in pharmaceutical alternatives to plasma products. Knowledge of these products and their indications for their use is critically important for transfusion consultants such that the most appropriate and best option is ultimately chosen for the patient in need. Given these developments and the ever-changing nature of transfusion therapy, the aim of this paper is to review the current state of, and recent advances in, plasma and cryoprecipitated component therapy in order to ensure that our patients are receiving the best and most appropriate product for their clinical situation.

Keywords: Plasma; cryoprecipitate; plasma derivatives; component therapy

Received: 28 February 2021; Accepted: 15 March 2022; Published: 31 March 2022.

doi: 10.21037/aob-22-7

View this article at: https://dx.doi.org/10.21037/aob-22-7

Introduction

Plasma is a versatile and frequently used blood product with a myriad of uses. This, along with the variety of preparations and plasma derived products available, can lead to confusion for clinicians and blood bankers alike when trying to select the most appropriate product for patients. The goal of this review is to provide a clear and comprehensive overview of the different plasma and plasma derived products that are available, as well as the indications and expected results from their use. For the purposes of this review, regulations and standards referred to will apply specifically to those in the US; different products, technologies, and guidelines may be in use in other countries.

Plasma for transfusion

Overview

In the most general terms, plasma simply refers to the liquid portion of blood. However, a deeper look into its composition and function reveals it to be anything but simple. Containing numerous proteins (including albumin), coagulation factors, complement, immunoglobulins, and enzymes (1), plasma contains much of what helps us stop bleeding, prevents us from clotting, and keeps our immune systems functioning. Because there are so many different components with different half-lives and optimal storage conditions, different methods of processing, manufacturing

and storing plasma and plasma derived products are essential for optimal product function. In this section we will start off by discussing plasma collection and move on to review each of these components and discuss the production and storage conditions for that component. Cryoprecipitate, a plasma derivative, will be briefly and separately discussed in a dedicated section.

Plasma collection

Plasma donors are held to the same eligibility requirements as all other blood donors as specified by the US Food and Drug Administration (FDA) (2). In addition to being healthy and well at the time of donation and completing the Donor Health and History Questionnaire, individuals who plan to donate plasma products must be male, nulliparous females, or females who have been screened and found to be negative for human leukocyte antigen (HLA) antibodies after pregnancy. This final requirement is a fairly new addition to donor screening and serves as an important strategy to decrease the incidence of transfusion related acute lung injury (TRALI) (3). TRALI has historically been a leading cause of transfusion associated death and is attributed to the presence of HLA-antibodies in donated plasma products. TRALI will be discussed in more detail in the section regarding adverse reactions to transfusion.

Plasma can be collected in two ways: as part of a whole blood donation or by apheresis. Whole blood derived products make up the majority of plasma for transfusion in the US (3). After a unit of whole blood is collected from a healthy donor, the entire collection is centrifuged to separate the components into red cells, and platelet rich plasma. That platelet rich plasma is transferred into a satellite bag away from the red cells and centrifuged again to further separate it into platelets and plasma. In an apheresis donation, only plasma is collected, and the remainder of the blood components are returned. This process also uses centrifugation to separate the plasma from the rest of the blood and leukoreduces the product in the same process (4). Volume can be extremely variable from unit to unit depending on the method of collection and can range from 250–300 mL (average volume) to 400–600 mL for a unit collected by apheresis. After plasma is obtained by either method of collection, it then undergoes storing and/or product modification and is labeled accordingly.

Plasma products

Fresh frozen plasma (FFP)

FFP is the most well-known plasma product and the one most requested by clinicians. It can be prepared from either whole blood or apheresis collections, and must be frozen at –18 ℃ within 8 hours of collection. This short time interval is critical for preserving the function of the more labile coagulation factors (Factor V, Factor VIII). After freezing, FFP can be stored for up to 1 year at ≤–18 ℃, or with special FDA approval, for up to 7 years at –65 ℃ (3).

At the time of use, the FFP is thawed, either in a water bath at 30–37 ℃, or utilizing another FDA approved thawing device. Once it has been thawed, its shelf life is reduced to 24 hours if stored at 1–6 ℃, or 4 hours if stored at 20–25 ℃. It can also be converted to Thawed Plasma and stored for a total of 5 days at 1–6 ℃ if the product has been prepared in a closed system.

FFP contains adequate levels of all coagulation factors including Factor V and Factor VIII as well as antithrombin and ADAMTS13 (1).

Plasma frozen within 24 hours after phlebotomy (PF24)

PF24 is defined as plasma that has been stored at 1–6 ℃ within 8 hours of collection and frozen to –18 ℃ between 8 and 24 hours after collection. It can be prepared from both whole blood derived plasma or apheresis plasma, and is produced when there are logistical, technical, or transportation constraints that prevent freezing within 8 hours (5). With the move to testing donors for HLA-antibodies prior to using their donated products, the amount of PF24 being produced has increased. After collection, donor testing is performed, and if there are antibodies present, that product is removed from the donation pool and not frozen. Awaiting this testing delays freezing of the product, and therefore, products are greater than 8 hours from the time of collection when frozen (6).

PF24 is thawed in the same manner as FFP at the time of use and has the same storage and outdate requirements. This product can also be relabeled as Thawed Plasma and be stored for an additional 4 days at 1–6 ℃ (1).

Compared to FFP, PF24 contains decreased levels of Factors V and VIII as well as Protein C but is otherwise equivalent (7,8).

PF24 held at room temperature up to 24 hours after phlebotomy (PF24RT24)

PF24RT24 is plasma collected by apheresis or from whole

blood that is held at room temperature for up to 24 hours and then stored at –18 ℃ for up to 1 year (1). Unlike PF24, this product is not refrigerated prior to freezing.

Thawing standards, post thaw storage, and outdating are the same as FFP. Coagulation factors are present in similar quantities as FFP with the exception of Factors V and VIII, and Protein S which are reduced (9).

Plasma cryoprecipitate reduced

Also referred to as "cryo-poor plasma", this plasma product is what is left after cryoprecipitate is collected from whole-blood derived FFP. The frozen FFP is partially thawed to 1–6 ℃, the precipitate is removed, and the remaining plasma must be refrozen with 24 hours (1). Cryoprecipitate will be discussed in detail in a later section.

The standards for storing and thawing plasma cryoprecipitate reduced are the same as the plasma products previously discussed.

The removed cryoprecipitate contains large amounts of Factors VIII and XIII, fibrinogen, and von Willebrand factor, so it follows that the remaining plasma has reduced levels of these factors. The levels of other factors present are comparable to FFP (3).

Thawed plasma

As discussed in the above sections, thawed plasma is FFP, PF24, PF24RT24 or plasma cryoprecipitate reduced that has been thawed and stored at 1–6 ℃ for greater than 24 hours. After the initial 24 hours, this product can be relabeled and stored at 1–6 ℃ for an addition 4 days (5 days total storage). This product is not licensed by the FDA but is recognized by the AABB and regulation and labeling requirements are included in the AABB Standards (Standard 5.7.4.12) (10).

Thawed plasma has adequate levels of non-labile factors with decreased amounts of Protein S and Factors, V, VII, and VIII. It can be used as a replacement fluid for patients undergoing therapeutic plasma exchange (TPE), especially for thrombotic thrombocytopenic purpura (TTP), or in bleeding patients with emergent need for plasma (3).

Liquid plasma

Unlike other plasma products, liquid plasma is unique in that it is never frozen. This product is formed when a unit of whole blood undergoes centrifugation and the plasma is removed. This can be done at any time during the acceptable storage period for whole blood, and the liquid plasma is stored at 1–6 ℃ for up to 5 days after the expiration of the whole blood unit. Therefore, the expiration date of the liquid plasma depends on the preservative solution for the whole blood unit from which it was derived. Whole blood that was stored in acid-citrate-dextrose (ACD)/citrate-phosphate-dextrose (CPD) or citrate-phosphate-double dextrose (CP2D) has an expiration date of 21 days, so the liquid plasma collected from that unit expires after 26 days. If the plasma is obtained from a unit of whole blood stored in citrate-phosphate-dextrose-adenosine (CPDA-1), the expiration date is 40 days following collection (4).

Factor levels in liquid plasma are normal initially but do decrease over time (11). Of note, this product may contain viable lymphocytes and require irradiation prior to transfusion to eliminate the risk of transfusion associated-graft versus host disease (TA-GVHD) (3).

Plasma derivatives

In addition to being utilized in the form of plasma, FFP is used to produce numerous products including albumin, intravenous immunoglobulin (IVIG) [formally labeled immune globulin (intravenous)] and factor concentrates. The frozen product is sent to a manufacturer who thaws the plasma and combines them into a large pooled lot. Using a process called Cohn fractionation, the plasma is processed and purified to form the desired products. The purification steps are commonly performed using immunoaffinity columns impregnated with factor specific antibodies (or in the case of some Factor VIII products, a von Willebrand factor antibody). As the plasma passes through the column the target factor adheres to the antibody, and the remaining plasma passes through. The factor is then eluted from the antibody to form a concentrated product (3).

Plasma product modifications

Numerous safety measures are in place to protect recipients of blood products from the time of collection through transfusion. Pre-donation questionnaires and physical examinations are in place to protect both the donor and the recipients of the donated product, and significant infectious disease testing is performed on the collected products. Despite this extensive screening and testing, there is still a very small but real risk of transfusion transmitted disease from both known and emerging pathogens (12). In order to attempt to mitigate this risk, additional product modification in the form of various types of pathogen inactivation can be performed prior to transfusion.

Pathogen reduction treated plasma

Although pathogen reduction technology is most frequently associated with platelets, it is also approved for and performed on plasma products. The INTERCEPT System from Cerus Corporation is the only system approved in the US by the FDA for pathogen reduction (3). It utilizes a psoralen based photoactivator (amotosalen) and ultraviolet A (UVA) light to disrupt nucleic acids present in pathogenic organisms as well as leukocytes. Because of this effect on leukocytes, this process also eliminates the need for irradiation in treated products to prevent TA-GVHD.

INTERCEPT is approved for use with platelets and plasma in the US, and it has been shown that post-treatment levels and activity of factors in plasma are equivalent to untreated plasma (13).

Solvent/detergent (S/D) treated plasma

In contrast to the pathogen reduction technology described above, S/D treatment of plasma does not affect the nucleic acid of cells and pathogens, but rather disrupts the cell membranes and viral envelopes (14). This product is produced by pooling hundreds of units of donated plasma that have been tested for infectious diseases and non-enveloped viruses. The pool plasma then undergo treatment with a solvent (1% tri-n-butyl phosphate) and detergent (1% Triton X-100) that disrupts the lipid membranes/viral envelopes (3). Pooling of such large volumes of plasma also serves to dilute any antigens that may be present in some of the units responsible for allergic reactions to transfusion, or HLA antibodies implicated in TRALI (12).

S/D plasma is packaged in uniform units of 200 mL and are ABO blood group specific. Just like other plasma products, it can be stored frozen at –18 ℃ for 12 months, and after thawing should be used within 24 hours. It is not typically considered for conversion to thawed plasma as other plasma products are, however a recent study showed that it is equivalent to thawed plasma from other sources for up to an additional 4 days after thawing (5 days total) (12).

The majority of the coagulation factors present in S/D plasma are reduced between 5–15% causing a clinically insignificant decrease in their activity levels. Factor VIII is reduced by approximately 20% and levels of Protein S and alpha-2 antiplasmin are significantly reduced. Overall, S/D plasma is largely equivalent to FFP (14).

Methylene blue pathogen inactivation

Methylene blue pathogen inactivation using the THERAFLEX MB-plasma system from Maco-Pharma is a methodology for pathogen inactivation used primarily in Europe. It is not currently approved for use in the US (3).

This process is similar to pathogen reduction using the INTERCEPT system but instead of using amotosalen, methylene blue is added to thawed FFP and activated using white light. After the activation, the methylene blue is removed by filtration and the plasma is refrozen (15). Thawing of the frozen plasma product prior to methylene blue addition is important to release any intracellular viral particles so they are exposed to the inactivation process.

Methylene blue treated plasma products are safe but contain 10% to 35% lower levels of Factor VIII and fibrinogen than plasma that has not been treated by this methodology (16). While it is effective for pathogen inactivation, primarily on enveloped viruses with some effect on non-enveloped viruses and bacteria, other methods provide a more clinically effective plasma product (15).

Laboratory studies for determining bleeding risk

Patients may require plasma administration in a variety of clinical situations including congenital or acquired factor deficiency, anticoagulation therapy, or coagulopathy related to an underlying disease state. Aside from knowing the patient history, it is important to review basic coagulation laboratory results to determine the best and most appropriate therapy for each patient.

Since the goal of plasma administration in the settings of both bleeding prophylaxis or current active bleeding is to replace or supplement absent or deficient coagulations factors, it is important to confirm that there is indeed a deficiency to correct, and what degree of correction is indicated. Following coagulation studies also allows for monitoring after transfusion to determine the effectiveness of the interventions. The most commonly utilized coagulation tests to determine the necessity of plasma transfusion are the prothrombin time (PT) and international normalized ratio (INR), and the activated partial thromboplastin time (aPTT).

The PT is performed using patient plasma (containing or lacking the coagulation factors present in the patient). The test evaluates the activity of the coagulation factors in the "extrinsic" and "common" coagulation pathways by incubating citrated patient plasma with tissue factor and measuring the time to clot formation after adding excess calcium chloride. Prolonged PTs indicate decreased levels or function of Factors VII, X, V, II, and/or I (17). In order for the PT to be affected, the factor(s) that are deficient/

defective must be functioning at <30% activity. Therefore, mild factor deficiencies will not be picked up with this testing.

The INR allows for comparison of PTs between laboratories by accounting for differences in reagents and instrumentation. It is a calculated value which utilizes the PT, the average normal PT for that laboratory, and the international sensitivity index (ISI) that has been determined for the combination of reagents and instrument used to obtain the PT. The INR itself was not designed to be used as a marker of bleeding risk, but rather as a way to compare PT values between laboratories (17). However, due to its extensive use, it has become an important marker in attempting to predict bleeding in patients. PT values >1.5–2.0 times the normal limits and INR values >1.7–2.0 are generally levels at which plasma transfusion can be considered depending on the clinical and bleeding status of the patient (18). Specific "trigger" values vary between institutions however.

Finally, aPTT is used to evaluate the activity of the coagulation factors making up the "intrinsic" coagulation pathway (Factors XII, XI, IX, and VIII) and the "common" pathway. This test is performed by incubating anticoagulated patient plasma (usually a citrate anticoagulant) with phospholipid and an activating agent such as silica, kaolin, celite, or ellagic acid (this activation step is the a in aPTT). As in the PT, excess $CaCl_2$ is then added and time to clot formation is measured. Also similar to the PT, prolongation of the aPTT requires factor activity to be below 15–35% depending on the factor affected (17). An aPTT that is prolonged more than 1.5–2 times the upper limit of the reference range is usually an indication to consider therapeutic plasma transfusion.

These laboratory values are important information to have when deciding on the appropriateness of plasma transfusion, but need to be interpreted in the clinical context of the patient at that time. For example, an INR of 1.4 is technically elevated (normal value is between 0.8 and 1.2) but plasma transfusion is not indicated at this value simply because the average INR of a unit of plasma itself is in this range (19). Transfusion at this level exposes patients to the risks of transfusion without providing any significant benefit in decreased bleeding risk.

Other examples of cases in which a patient may have abnormal coagulation studies without indication for plasma transfusion are patients on anticoagulants such as heparin or patients with a known factor deficiency. In these cases, reversal of the anticoagulant or specific factor concentrates (if available) would likely be more beneficial and effective than plasma transfusions (20). In addition, patients predisposed to bleeding and/or clotting due to underlying liver disease, antiphospholipid syndrome, etc. are also unlikely to receive benefit from regular plasma transfusion.

Indications for use

In the simplest terms, indications for plasma use can be broken down into two categories: prevention of bleeding or management of bleeding that is already ongoing. There are multiple subcategories within these areas which we will explore as well as the indications for the use of plasma as a replacement fluid in TPE and the use of plasma derivatives.

Anticoagulation reversal

One of the most well-known uses for plasma transfusion is anticoagulant reversal, and more specifically, reversal of vitamin K antagonists, i.e., warfarin. Warfarin works by inhibiting the enzyme vitamin K Reductase thereby preventing regeneration of the active form of vitamin K (21). The active form of Vitamin K is a required cofactor in the modification of glutamate residues of Factors II, VII, IX, and X as well as Protein C and Protein S. Therefore, inhibiting the regeneration of active vitamin K leads to decreased function of these factors and is demonstrated in laboratory testing by prolongation of the PT (and elevated INR) as well as the aPTT (22).

The low cost and convenience of the oral administration of warfarin is countered by the regular testing required to maintain a therapeutic (but not dangerously high) INR, possibly complicated dosing schedules and the impact that diet has on the effectiveness of the drug. Diets high in vitamin K blunt the inhibitory effect of the drug, and changes in diet often require changes in dosing. Given all of these limitations, warfarin still remains a frequently used drug in patients requiring anticoagulation because the reversal agents are readily available and relatively easy to administer.

A therapeutic INR for a person on warfarin is 2–3 or 2.5–3.5, depending on the indication for anticoagulation. When the value exceeds these goals, clinicians must decide if reversal is indicated, and if so, what method should be used. The first consideration is whether or not the patient is bleeding. In the absence of bleeding in a patient with an INR <10, current recommendations are simply to hold warfarin and continue to closely monitor the patient. In patients without bleeding and an INR >10, oral vitamin

K supplementation is recommended. Only when patients are bleeding is active replacement of vitamin K dependent factors recommended (23).

Four-factor prothrombin concentrate (4-FPCC) and plasma (24) are the two products of choice to reverse vitamin K antagonists in actively bleeding patients. Both contain Factors II, VII, IX, and X in adequate levels when administered in proper doses. If it is available, 4-FPCC is typically the treatment of choice in warfarin reversal for emergent procedures or large/life threatening bleeding having been shown to act more quickly than plasma. However, it is significantly more expensive than plasma, and therefore is not always available. It should also be noted that 4-FPCC has a higher thrombotic risk than plasma. No matter which product is used, IV vitamin K is recommended in addition to factor replacement (23).

In patients who require rapid vitamin K antagonist reversal for a procedure, plasma and vitamin K are typically preferred if the patient is able to tolerate the volume required. Discussion with transfusion medicine and/or pharmacy services at your local institution is recommended.

Plasma administration has little to no role in the reversal of other anticoagulants including heparin, direct thrombin inhibitors, and Factor Xa inhibitors. Given the mechanisms of action of these drugs, plasma has minimal impact on activity level of coagulation factors, and patients receive more benefit from administration of the antidotes to the specific drugs if available (25).

Bleeding

There are numerous possible causes of bleeding that may require transfusion support. Bleeding from both traumatic and non-traumatic causes as well as congenital bleeding disorders can be severe enough to require transfusion of not only red blood cells, but also platelets and plasma. Given that whole blood is not commonly used or available in the majority of institutions in the US, it is important to understand how to administer separate blood components in a way that recapitulates whole blood lost by the patient without exacerbating coagulopathy or hemodilution.

Massive bleeding in both trauma and non-trauma settings are largely approached in the same way. The majority of Massive Transfusion Protocols (MTPs; initiated when there is actual or anticipated loss of 10 or more units of blood) are designed to provide a 1:1:1 ratio of red cells:plasma:platelets (26). The exact contents of these MTPs differ by institution, and sometimes within institutions based on the cause of the massive bleeding, but all acknowledge the importance of providing adequate amounts of plasma and therefore coagulation factors.

There have been many studies investigating the optimal ratio of products to transfuse and when to transfuse them in cases of massive hemorrhage, but there is little consensus beyond the above mentioned typical product ratios. It is important to continue to monitor not only the patient's vital signs and body temperature during these massive transfusion events, but to continue to follow their laboratory values to make any adjustments or additions such as additional plasma or the use of cryoprecipitate.

In the case of bleeding in a patient with a congenital bleeding disorder, plasma is an option, but should be considered as a second choice if a factor concentrate for the specific deficient factor is available. The use of a factor concentrate rather than plasma has many possible benefits. First, the production of factor concentrates significantly decreases the risk of transfusion transmitted diseases. Second, the volume of infusion is smaller with factor concentrates than plasma. Finally, as the name states, factor concentrates are a concentration of the specific factor that is deficient or dysfunctional and leads to higher activity levels in the recipient than plasma (27).

Currently, factor concentrates are available for all factors with the exception of Factor II and Factor XI. Other factor concentrates, such as Factor X, are commercially available, but not always stocked because the need is so low. If a factor concentrate does not exist, or isn't available, plasma is an excellent substitute. If applicable, one can also consider 4-FPCC (27). Volume must be taken into consideration when treating factor deficiencies with plasma though, as we will address in the section on appropriate dosing of plasma products.

In patients with abnormal coagulation studies due to underlying disease (such as liver disease) there is no need for treatment if the patient is not bleeding. Unfortunately, there is a paucity of data related to use of plasma in these patients as prophylaxis for invasive procedures. Most institutions have developed internal guidelines pertaining to these cases, but more data is required to form definitive recommendations.

TPE

Plasma, and its derivative product albumin, are the primary replacement fluids used in TPE procedures (28). Albumin provides volume replacement as well as oncotic support after the removal of plasma in the majority of TPE procedures, however there are cases where replacement with plasma

is indicated. The most significant of these indications is TTP. In TTP, patients develop severe thrombotic microangiopathy due to an inhibitor to ADAMTS13 leading to accumulation of very large von Willebrand factor multimers (29). TPE with plasma replacement provides the dual benefits of removing the inhibitor, and replacing ADAMTS13 which is present at normal levels in plasma products.

Any of the plasma formulations described at the beginning of this review are adequate for replacement in TTP, but there are data showing that "cryo-poor" plasma may be associated with longer time to recovery and increased numbers of exacerbations, so it is not recommended as a first line replacement fluid if others are available (30).

Providing a continuous infusion of plasma (and therefore a continuous infusion of functional ADAMTS13) is recommended in cases where TPE is not immediately available.

Other indications for full or partial replacement with plasma in TPE treatments are conditions such as anti-glomerular basement membrane syndrome that may have a component of alveolar hemorrhage, and other thrombotic microangiopathies. Plasma can also be used if there are any indications that there is bleeding secondary to removal of coagulations factors in the plasma exchange; specifically, if there is bleeding during or after exchange (29). It should also be noted that in cases where there is concern for thrombosis, such as catastrophic antiphospholipid syndrome, full or partial replacement with plasma in combination with albumin should be considered. In this case, the concern is depletion of anticoagulant factors (Proteins C and S) rather than the levels of procoagulant factors.

There are benefits to replacing the plasma removed with donor plasma, but there are also risks that must also be taken into consideration. The most significant of these risks is the exposure of the recipient to large volumes of donor plasma from numerous different donors. Patients must be monitored for possible transfusion reactions, and these must be investigated as any other possible transfusion reaction would be investigated. Also present is the risk of citrate toxicity given that citrate is used both as an anticoagulant during the TPE procedure and in the transfused plasma products.

Dosing and administration of plasma products

As seen in the previous sections on coagulation testing and indications for plasma transfusion, providing the patient with enough plasma to address their underlying coagulation issues without placing them at risk for volume overload or giving unnecessary transfusions can be a tricky balancing act.

The majority of coagulation factors will provide adequate hemostasis at an activity level of 25–30%, so this is the goal that we hope to reach when transfusing plasma. Weight-based dosing is a strategy that provides patient-specific dosing based on each person's individual plasma volume.

Calculating a patient's plasma volume based on their height, body weight and hematocrit will allow one to calculate the most accurate volume of plasma for transfusion. In other words, a volume of transfused plasma equal to 30% of the patients' blood volume will replace 30% of the activity of all coagulation factors (31).

If only the patients' weight is available, a simpler, but less exact, formula will provide similar transfusion recommendations. Dosing plasma at 10–15 mL/kg also replaces approximately 30% of the coagulation factor activity, but may overestimate the volume infused.

Product selection and preparation

After determining the appropriate dose of plasma for transfusion, the product is thawed and prepared in the blood bank. When selecting products to prepare, one must consider ABO compatibility. Plasma is an acellular blood product, but does contain a variety of antibodies including ABO antibodies. When determining which plasma units are compatible, the interactions between these antibodies and the antigens must be considered or the patient is at risk of receiving an incompatible transfusion.

In the reverse of ABO matching for red blood cells, group AB plasma is "universal donor" plasma due to the absence of anti-A and anti-B antibodies (31). When the patient ABO type is known, the best plasma product for them is one that is ABO identical/ABO compatible. In cases of urgent or emergent transfusion when the ABO type of the patient isn't available, best practice is to supply AB plasma. This however, is not always possible. Given that only approximately 4% of people in the US are blood group AB, and that an even smaller number of these group AB individuals are plasma donors, large volumes of AB plasma are frequently not available or sustainable for long periods of transfusion. In these cases, practice has been to utilize plasma from group A donors. Studies have shown that there is no evidence of poorer outcomes or increase in mortality when group A plasma is administered to non-group A

patients in the setting of emergent, traumatic bleeding (32).

Liquid plasma, which is unique among the plasma products having never been frozen, potentially contains some intact red blood cells from the donor. This raises concern not of hemolysis, but rather of Rh(D) alloimmunization of the recipient in cases of transfusion of Rh(D)+ plasma to an Rh(D)- individual. For this reason, it is recommended that fresh/liquid plasma products be matched for Rh(D), especially in children or women of childbearing age (3). Plasma products that have been frozen have not shown significant residual Rh(D) antigen, and do not require matching for Rh(D) (33). Other non-ABO blood group antigens do not need to be considered when choosing a plasma product for transfusion regardless of the type of plasma. Donors are screened for red cell alloantibodies, and those with antibodies detected are excluded from the plasma donor pool. Therefore, crossmatching of plasma components is unnecessary.

After the appropriate product has been selected, the frozen products require thawing. Thawing can be performed by using water baths, dry tempering platforms, or microwave devices designed specifically for plasma thawing. Regardless of the device used, thawing must take place between 30–37 ℃ in order to preserve the functionality and safety of the product. Given that thawing can range from 10–30 minutes, having thawed or liquid plasma in inventory can be prudent in order to be prepared for cases of urgent or emergent transfusion. After the plasma product is fully thawed, the bag is carefully inspected to ensure its integrity, and if it is intact, it is ready to be released from the blood bank (3).

Consistent with transfusion requirements for other blood products, plasma must be transfused through a filter, and cannot be administered in the same line as anything except normal saline. The infusion must be completed within 4 hours after it has been started, although the rate of infusion will vary depending on the clinical status of the patient. In a stable adult, a unit of plasma can be safely infused over 30–120 minutes, and in stable pediatric patients, the recommended rate is over 2–3 hours. Patients at risk for volume overload, or those that have renal and/or cardiovascular deficiencies will likely require infusion over a longer period of time, even up to 4 hours (27).

Contraindications and complications in plasma transfusion

As with any blood product or medical therapy, there are risks associated with plasma transfusion. These risks include transfusion transmitted infections and transfusion reactions such as transfusion associated circulatory overload (TACO), TRALI, and allergic transfusion reactions. Each of these adverse events is relatively uncommon, but they should always be considered when deciding if a transfusion is warranted.

Infectious disease risk

Transfusion may transmit viruses, bacteria, parasites, and prions. The consequences of transmission of one of these diseases from a donor to a recipient can be severe, so multiple layers of screening and testing are used in an attempt to mitigate this risk. As a result, transfusion-transmitted diseases have thankfully become a rare complication of blood transfusion (31).

Donors are screened prior to donation though a detailed set of questions covering behaviors, medical histories, and travel histories that may put the donor at a higher risk for carrying, and therefore transmitting, an infectious agent. If the risk is deemed to be significant, the donor is unable to donate and is deferred either temporarily or indefinitely (34). Additional detailed discussion of donor product testing is beyond the scope of this review, but while a small risk of disease transmission is present, this has thankfully become a very rare occurrence.

TACO

TACO is a transfusion reaction that can occur with any blood product, including plasma. It is caused by vascular volume overload, and has a mortality rate of 5–15%. Patients most at risk are those who are at the extremes of age, or who have underlying cardiac dysfunction/risk for volume overload. Close monitoring of patients during their transfusion, especially those who are receiving large volumes of plasma, can lead to early recognition and treatment of volume overload. These patients can be treated with diuretics and supplemental oxygen, and future transfusions should be given in smaller volumes over longer periods of infusion (31).

TRALI

In contrast to TACO, TRALI is a noncardiogenic process leading to pulmonary edema. The mechanism is not fully understood, but is believed to be related to HLA and human neutrophil antigens (HNA) antibodies in transfused blood products containing plasma. TRALI mitigation strategies, including utilizing only male and nulliparous females (as well as females tested for the presence of HLA

or HNA antibodies after each pregnancy) as donors for plasma and plasma containing products and deferring any donors who have had products associated with TRALI, have significantly decreased the incidence of this potentially fatal reaction (3).

Allergic reactions

Allergic transfusion reactions range from mild to severe, though thankfully most fall into the mild-moderate range. They occur when there is a reaction between preformed antibodies in the recipient and antigen that is present in the transfused product. Mild-moderate allergic reactions are characterized by itching, rash, and/or urticaria. They typically resolve with cessation of the transfusion and administration of anti-histamines (31). These reactions are not uncommon, and aside from close monitoring and consideration of premedication with future transfusions, do not typically impact the ability to transfuse a patient in the future.

Severe allergic reactions are characterized by anaphylaxis (35). The most famous of these reactions is related to immunoglobulin A (IgA)-deficient patients who have developed anti-IgA antibodies who are transfused with blood products containing IgA. In these cases, patients can be transfused plasma products from other IgA-deficient individuals if they require transfusion (31).

In many cases, the cause of severe anaphylactic allergic reaction cannot be determined. In these cases, avoiding transfusion is always the safest course, but if this isn't possible, generous use of antihistamines and/or steroids is recommended along with slow infusion rates and very close monitoring.

In summary, plasma is a deceptively complex blood product that is often underestimated in its versatility. Understanding when to use, and when not to use, plasma and plasma products is extremely important in the management of bleeding patients or those who are at risk of bleeding. The purpose of this overview was to attempt to clarify some of the confusion surrounding these issues and to provide a review of the latest developments and recommendations in transfusion of these products.

Cryoprecipitated products

Overview

Prepared from thawing traditional plasma units (as described above) at 1–6 ℃, cryoprecipitated plasma products/derivatives are smaller volume (generally, an average of 15 mL/individual unit) and contain a more limited profile of procoagulants, most prominently fibrinogen and fibronectin (1). In addition, the cryoprecipitation process also yields a concentrated dose of Factor VIII, von Willebrand factor, and Factor XIII.

Cryoprecipitate components

The most widely used formulation is cryoprecipitated antihemophilic factor (AHF), often abbreviated as 'cryoprecipitate' or sometimes simply as 'cryo'. After thawing traditional plasma at 1–6 ℃, the precipitate is extracted and frozen within an hour after removal. US standards indicate that each unit of cryoprecipitate must contain at least 80 IU of Factor VIII and at least 150 mg of fibrinogen (1). Beyond these single units, in recent years a pre-storage pooled product has been available from blood suppliers in the US and internationally, which typically consists of five individual units pooled together at donor sites and issued to hospital transfusion services in the pre-pooled state (36). Similar to processes used for plasma, there are also applications of pathogen-reduction technologies to cryoprecipitated products (37).

Laboratory studies for determining bleeding risk and cryoprecipitate use

As a component with a limited scope of procoagulants, the laboratory studies used to influence decision-making for cryoprecipitate tend to be much more limited as well and much more specific in scope. As primarily a fibrinogen concentrate, fibrinogen levels (either via the Clauss method or PT-derived method) are an important determinant for utilization of cryoprecipitate. Thrombin times and/or reptilase times may be equally important for use of cryoprecipitate in the setting of dysfibrinogenemia (38). While no true prospective studies have been performed, goals for active bleeding or prophylaxis aim to increase fibrinogen to above 100–150 mg/dL for most indications, with some authors suggesting even higher goals for clinical settings such as hypofibrinogenemia associated with major obstetric hemorrhage (39). This will be discussed further in the section on 'Indications for use'.

Because of its additional contents, and in the absence of specific factor concentrates, Factor XIII levels can also be of importance in determining whether cryoprecipitate infusion may be appropriate (40). Historically, cryoprecipitate

was the main source for Factor VIII and von Willebrand factor, and thus studies of these factors were critical to determine appropriateness of this component. However, and as discussed later, use of cryoprecipitated products for Hemophilia A and von Willebrand disease has largely been abandoned and replaced by therapy with specific factor concentrates (41).

Indications for use

Fibrinogen replacement

Due to its small volume and concentrated nature, cryoprecipitate products remain the treatment of choice for acquired disorders of fibrinogen, most prominently hypofibrinogenemia, but also dysfibrinogenemia. In bleeding individuals, who may have consumption of fibrinogen, dilution of fibrinogen, or some combination of the above, most guidance and experience-based approaches suggest cryoprecipitate use to maintain fibrinogen levels >150 mg/dL (36). One important exception is bleeding associated with major obstetric hemorrhage, wherein rapid and profound decreases in fibrinogen can be seen. In such settings, some authors and guidance have suggested targets of >200–250 mg/dL to assure appropriate hemostasis (42). Finally, there are no strong recommendations for fibrinogen goals for prophylactic, non-bleeding patients (e.g., in the setting of surgical interventions), but many authors and guidance suggest considering transfusion, if appropriate, once fibrinogen levels drop to <100 mg/dL (36).

With the evolution of dedicated, pharmaceutical-grade fibrinogen concentrate therapies, most guidelines suggest use of such specific therapies for congenital fibrinogen disorders, particularly entities such as congenital afibrinogenemia or hypofibrinogenemia (40). However, are such purified concentrates more appropriate, or even superior to, cryoprecipitated products for treating acquired disorders? At least one clinical trial in the setting of cardiac surgery found non-inferiority of fibrinogen concentrate in this setting, and with the added benefit of less likelihood of transfusion-transmitted illness due to the purification associated with preparing this concentrate (43). Nonetheless, and to date, there are no compelling data suggesting that fibrinogen concentrates are superior to cryoprecipitate, and the advent of a pathogen-reduced product has reduced concerns for infectious disease transmission. As such, and until better data are available, continued use of cryoprecipitate for acquired fibrinogen disorders appears safe and appropriate (39).

Factor XIII replacement

Individuals can (rarely) present with bleeding due to congenital Factor XIII deficiency or, somewhat more commonly, due to acquired defects (e.g., in the setting of disseminated intravascular coagulation) (44). While a dedicated, purified Factor XIII concentrate is available for congenital deficiencies, cryoprecipitate would be appropriate if such a concentrate is not available, and for acquired forms of Factor XIII deficiency.

Uremic bleeding

Increasingly, there is strong evidence that renal failure and uremia contribute to platelet dysfunction associated with potentially severe bleeding. While platelet transfusion is not of particular benefit in this setting (since transfused platelets acquire a similar defect), data suggest that 'overloading' von Willebrand factor via cryoprecipitate transfusion may help overcome acquired uremic defects (45).

Bleeding associated with tissue plasminogen activator (tPA)

Individuals with thrombotic occlusive events (e.g., stroke) may be administered tPA to 'lyse' the thrombus and restore normal blood flow. Unfortunately, in upwards of 10% of tPA uses, severe bleeding complications can arise, including gastrointestinal hemorrhages and even hemorrhagic strokes. Because the mechanism of action of tPA is to activate fibrinolytic pathways, expert guidance suggests cryoprecipitate may be of benefit in promoting hemostasis in such circumstances, by replenishing fibrinogen and Factor XIII (46).

Hemophilia A and von Willebrand disease

With the evolution of dedicated, purified factor concentrates (some even fully recombinant), the use of cryoprecipitated products for treating hemophilia A or von Willebrand disease is sharply in decline. However, in emergency situations where a dedicated or purified factor concentrate may not be immediately available, cryoprecipitate can certainly be employed to replenish Factor VIII and/or von Willebrand factor.

Dosing and administration of cryoprecipitated products

General considerations

As a small volume product, with limited ABO antibodies, there are reports of ABO incompatible cryoprecipitate products being administered without serious adverse

events in adults (47). Nonetheless, whenever possible (and certainly for small recipients like neonates and children), ABO compatible products are preferred (1). As an acellular product, there is no need to Rh match and also no need to irradiate cyroprecipitated products. Given small component volumes, and in order to achieve meaningful increment in procoagulants like fibrinogen, cryoprecipitated products are typically pooled prior to administration for adults, while individual units may be used for children. Once thawed, cryoprecipitated units should not be refrigerated, lest the components re-precipitate (48). In the US, if a product is pooled on site post-thawing, then such components expire within 4 hours of thaw, while pre-storage pooled products have a 6-hour expiration window (1,2). Pathogen-reduced products with much longer expiration periods are being studied (37).

Fibrinogen replacement

The most comprehensive data regarding appropriate dosing for cryoprecipitate derive from fibrinogen replacement studies. There are very useful equations available, which can be employed to calculate an exact dose of cryo, typically requiring knowledge of a patient's: pre-infusion fibrinogen levels, goal levels, plasma volume, and the average content of fibrinogen in an individual cryo unit. Online applications and calculators are available to assist in dosing (49). If formal data or calculators are not available, a general rule of thumb for adult patients is that one individual unit per 10 kg body weight of the recipient should increase fibrinogen levels by 50–75 mg/dL (1). Thus, for most patients, starting doses of 10 units (or a 10-unit pool) is appropriate.

Other acquired defects—uremic bleeding, tPA reversal, FXIII replacement

There are limited prospective data on appropriate starting doses for cryoprecipitated products for other acquired forms of bleeding. For uremia, most evidence-based guidance suggests starting with a 10-unit pooled dose for adult patients with repeated doses as clinically warranted based on degree of bleeding, recovery of renal function, and/or implementation of other, more definitive therapies (e.g., renal replacement therapy) (45). For tPA reversal, a similar approach of 10 units pooled cryoprecipitate is appropriate in order to achieve replacement of at least 2,000 mg of fibrinogen in this setting. Repeated dosing would also be considered for ongoing hemorrhage or evidence of persistent hypofibrinogenemia (46). Finally, generally only low levels of Factor XIII are required to maintain normal hemostasis. As such, guidance suggests 3–5 units of cryoprecipitate is likely sufficient to achieve normal clot formation, with repeated doses as clinically appropriate (40).

Hemophilia A and von Willebrand disease

As discussed previously, purified human-derived or recombinant factor concentrates have become the preferred, first-line therapy for individuals requiring transfusion or infusion therapy. Such products should always be employed if available. However, in settings where there is bleeding or need for urgent transfusion, and a dedicated concentrate is not immediately on hand, then cryoprecipitate can certainly be utilized. Current guidance suggests the cryoprecipitate dosage for Factor VIII should be as follows for adults (1):

$$Number\ of\ bags = \frac{Desired\ increase\ in\ FVIII \times 40 \times Body\ weight\,(kg)}{Average\ FVIII\ content\ per\ cryo\ unit} \quad [1]$$

For the above calculation, it is prudent to recall that each unit of cryoprecipitate should contain at least 80 IU of Factor VIII per regulatory standards. Regarding von Willebrand factor replacement with cryoprecipitate in adults, and similar to other approaches, guidance suggests employing 1 unit of cryo per 10 kg body weight while closely following laboratory studies and clinical status after dosing (1). Pediatric dosing for the above generally suggests 1–2 units/10 kg body weight (1).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Paul D. Mintz) for the series "Transfusion Therapy: Principles and Practices" published in *Annals of Blood*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-22-7/coif). The series "Transfusion Therapy: Principles and Practices" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob-22-7
Cite this article as: Horstman EE, Tormey CA. Plasma products for transfusion: an overview. Ann Blood 2022;7:4.