Which is the preferred blood product for fibrinogen replacement in the bleeding patient with acquired hypofibrinogenemia—cryoprecipitate or fibrinogen concentrate?

Melissa M. Cushing,[1] *Thorsten Haas*,[2] *Keyvan Karkouti*,[3,4] *and Jeannie Callum*[5,6,7]

The importance of the targeted treatment of acquired hypofibrinogenemia during hemorrhage with a concentrated fibrinogen product (either cryoprecipitate or fibrinogen concentrate) cannot be underestimated. Fibrinogen concentrate is a pathogen inactivated, pooled product that offers a highly purified single factor concentrate. Cryoprecipitate is a pooled product that comes with a spectrum of other coagulation factors which may further enhance (additional procoagulant effect) or even disturb (prothrombotic risk) hemostasis. The pros and cons of each product are discussed.

PRO FIBRINOGEN CONCENTRATE: FIBRINOGEN CONCENTRATE IS THE PREFERRED BLOOD PRODUCT FOR FIBRINOGEN REPLACEMENT IN THE BLEEDING PATIENT WITH ACQUIRED HYPOFIBRINOGENEMIA

Through this section of our debate, we will attempt to convince you to abandon cryoprecipitate (if you have not already done so) for the management of hemorrhage in the presence of acquired hypofibrinogenemia (fibrinogen level less than 1.5-2.0 g/L). It is crucial for the safety of future generations of transfusion recipients that all blood products transfused are pathogen inactivated (where available, safe, and effective).[1] Although there are numerous hurdles to the implementation of pathogen-inactivation technologies across all manufactured blood products and components,[2] there is ample evidence to support the transition to pathogen-reduced fibrinogen concentrates and to archive cryoprecipitate. Based on recent comparative data,[3] fibrinogen concentrates are rapidly replacing cryoprecipitate across Canada due to safety, efficacy

From the [1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York; the [2]Department of Anesthesia, Zurich University Children's Hospital, Zurich, Switzerland; the [3]Peter Munk Cardiac Centre and [6]Laboratory Medicine Program, University Health Network; the [4]Department of Anesthesia and Pain Management, University Health Network, Sinai Health System, Women's College Hospital, University of Toronto; the [5]Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, and the [7]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada.

Address reprint requests to: Melissa M. Cushing, MD, 525 East 68th Street, Box 251, New York, NY 10065; e-mail: mec2013@med.cornell.edu.

Received for publication November 8, 2019; revision received November 12, 2019, and accepted November 12, 2019.

doi:10.1111/trf.15614

© 2019 AABB

TRANSFUSION 2020;60;S17–S23

TABLE 1. Summary of the differences between the two products for numerous attributes

Attributes	Cryoprecipitate (4 grams of fibrinogen)	Fibrinogen concentrate (4 grams of fibrinogen)
Storage	Frozen	Room temperature or refrigerated storage, Lyophilized
Shelf life	1 year	3 years
Volume	Variable based on manufacturing (220-300 mL)	200 mL
Donor pool size	5-10	1000s
Rapid preparation/injection	Not currently, but possibility for pathogen reduced cryoprecipitate stored at room temperature in the future	Yes
Near patient storage	Not currently, but possibility for pathogen reduced cryoprecipitate in the future	Yes
Pathogen reduction	Not currently, but possibility for pathogen reduced cryoprecipitate in the future	Yes
Variability in fibrinogen content	Highly variable	Uniform
Impurities	Numerous, impact unknown some may be beneficial for hemostasis (e.g., factor XIII), but others a risk for thrombosis (e.g., factor VIII, platelet microparticles, von Willebrand factor)	Highly purified, but some contain higher levels of FXIII
Phases of hemostasis addressed	All	Only fibrin polymerization
Impact on platelet production	Loss of 1 unit of platelets per 1 unit of cryoprecipitate in some manufacturing settings	NA
Manufacturing cost	Low, but provision of a pooled and pathogen inactivated product will come at an increased cost	High

and logistical considerations. Our European colleagues have already made this logical transition and we would like to highlight that not one of them has switched back to cryoprecipitate post-transition. There are three parts to our argument for the use of fibrinogen concentrates over cryoprecipitate: 1) product superiority, 2) recipient safety, and (3) logistical advantages. The overall comparison between the two fibrinogen replacement products can be seen in Table 1.

Product superiority

For this first section of the debate we would like to highlight the product differences between cryoprecipitate and fibrinogen concentrate to convince you of superiority of the latter for our patients. Fibrinogen concentrates are lyophilized and some can be stored at room temperature allowing for near-patient storage and rapid preparation. They have a longer shelf-life (3 years versus 1 year) which is particularly important for small rural hospitals which are only faced with a need for fibrinogen replacement once or twice a year. The product can be used for up to 24 hours (versus 4-6 hours for cryoprecipitate) after preparation/reconstitution, making waste less likely.

The product-specific advantage is the purity and uniformity of the product. Cryoprecipitate contains numerous impurities including platelet microparticles and fibronectin, as well as coagulation factor VIII and von Willebrand factor.[4] It would be unlikely that the infusion of all those extra proteins will come risk free. If cryoprecipitate enthusiasts wish to claim hemostatic superiority, they have to concede that there might also be "thrombotic superiority." In addition to the concerns about these impurities, cryoprecipitate also has highly variable amounts of fibrinogen; indeed, one-third of 10-pools in Canada are predicted to have less than 3 grams of fibrinogen (personal communication based on fibrinogen content in quality control samples, Dana Devine PhD, Canadian Blood Services). Lastly, there is no improvement in hemostatic efficacy for cryoprecipitate over fibrinogen concentrate. A recently completed randomized controlled trial at 11 centers found fibrinogen concentrate to be non-inferior to cryoprecipitate in 735 patients with acquired hypofibrinogenemia and bleeding after cardiac surgery.[3] The hemostatic primary endpoint was the cumulative number of allogeneic blood products transfused in the first 24 hours after cardiopulmonary bypass. All other hemostatic endpoints reported in the trial were also similar between the two arms of the study. This finding means we can confidently switch to fibrinogen concentrate without seeing more bleeding in this setting.

Although fibrinogen's importance has been well established in in vitro and observational studies, the clinical efficacy of fibrinogen replacement has proven difficult to demonstrate in a well-designed randomized clinical trial, when compared against placebo. A review of recently published randomized controlled trials assessing the use of fibrinogen concentrate in the perioperative setting described great variation in the study design of those trials.[5] Some flaws in the published studies were that nonbleeding patients and patients not suffering from hypofibrinogenemia

were included. In addition, many subjects were underdosed or did not reach normal fibrinogen levels after study intervention.[5] However, when the authors only evaluated trials that treated clinically relevant bleeding in patients with hypofibrinogenemia, the fibrinogen arm had decreased bleeding tendency and transfusion requirements versus comparative treatment.

Recipient safety

Let us now move on to the second section of this debate: recipient safety. It is critical that we think ahead. Prevention of blood pathogen transmission will almost certainly be cheaper for the health care system. We cannot forget our collective histories of emerging pathogens. Over 10,000 men with hemophilia in the United States were infected with the human immunodeficiency virus (HIV) from blood transfusions. Over 60,000 patients in Canada were infected with hepatitis C from transfusions. Cost analyses comparing cryoprecipitate to fibrinogen favors cryoprecipitate, however these analyses failed to include the potential costs of future emerging pathogens.[6] This is the primary driving force for switching to fibrinogen concentrate so it is concerning and surprising that it was excluded from economic analyses. In fact Kleinman et al. published a model of the impact of an emerging pathogen in the Canadian blood system and predicted that a large number of patients will be infected by the time we realize we have a new blood borne pathogen and put blood testing strategies in place.[7] The model suggested plasma products will contribute approximately a quarter of infections and the costs of inaction will be substantial. In addition to emerging pathogens, we need to consider the genetic evolution of known pathogens allowing escape from molecular detection technologies. Indeed, there have been transmissions of high viral load HIV units due to mutations at the priming sequence for nucleic amplification technology (NAT) testing.[8] We came together as a blood transfusion community over a decade ago for a consensus conference on decisions regarding the transition to safer blood products such as fibrinogen concentrates.[1] The panel concluded that: "Given the recognition of transfusion-transmitted agents that are entering the blood supply and the risk of emerging infectious threats, the Panel believes that pathogen inactivation should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available."

As mentioned in the superiority section, the impurities in cryoprecipitate may contribute to a greater thrombotic risk for this product. In the FIBRES trial comparing fibrinogen concentrate to cryoprecipitate in adult cardiac surgery patients,[3] the investigators found a non-significant trend towards a lower risk of arterial and venous thromboembolic complications with fibrinogen concentrates as compared to cryoprecipitate (odds ratio 0.70, 95% confidence interval 0.42-1.20). In a randomized trial of fibrinogen concentrates versus cryoprecipitate in patients undergoing abdominal surgery for pseudomyxoma peritonei, the observed thrombosis rate was higher in the cryoprecipitate arm (7/23–30.4%) versus the fibrinogen concentrate arm (0/22–0%).[9] The overall risk of thrombosis for patients who receive fibrinogen concentrate is most likely extremely low; a recent review of randomized controlled trials that included over 700 patients who received fibrinogen concentrate summarized that no study reported an increase in the rate of perioperative thrombosis in the fibrinogen versus comparator arms.[5]

Logistical advantages of fibrinogen concentrate

Finally, let us consider the logistical advantages of fibrinogen concentrate over cryoprecipitate. We need to discuss the impact of the cryoprecipitate manufacturing process on the blood suppliers, the hospitals, and the bedside clinical team.

First, let us consider the impact of the manufacturing of cryoprecipitate on the blood suppliers in North America where this product is still in common use. For every unit of cryoprecipitate produced, there is a loss of a unit of platelets (for regions where platelets are manufactured using the buffy coat method), a unit of plasma (cryoprecipitate is made from thawed plasma), or both. This is an important loss because it aggravates platelet shortages and reduces the supply of plasma for transfusion or as source for production of fractionated blood products (particularly intravenous immunoglobulin, where shortages have been problematic). In addition, every cryoprecipitate unit made from whole blood filtered production method results in a co-produced inferior red cell unit that is associated with an increase in recipient mortality[10] and higher levels of hemolysis.[11] Cryoprecipitate production is itself human resource intensive if pooled at the blood supplier or at the hospital.

Second, let us discuss the impact of cryoprecipitate on hospital blood bank laboratories. In all the blood banks across the planet where cryoprecipitate is still in use, there are additional cryoprecipitate freezers plugged into power sources that must be monitored 24/7. The inventory management is logistically heavy with multiple units needed per adult dose. The product has a short life-span after thawing (less than 4-6 hours) and therefore can only be thawed after the blood bank is notified of a hemorrhaging patient with hypofibrinogenemia. It takes a minimum of ten minutes to thaw in a water bath. In regions where it is not pre-pooled by the blood supplier, the technologists must pool this both electronically and physically—each task taking 10-15 minutes. We argue that it would be better for these technologists to be doing something else for the hemorrhaging patient such as completing their laboratory testing or preparing other components. And if the patient is not fortunate to survive their resuscitation while awaiting the product preparation, the product is almost certainly destined for discard due to the short expiration time after

production. Actually, one in five pools of cryoprecipitate lands in the garbage[12] —highlighting the obvious problem that perhaps patients also are dying before the opportunity to get it.

Lastly, let us go to the bedside where we have had a hemorrhaging patient that has been waiting for cryoprecipitate for 30 minutes. And do not forget the possibility that the patient might have already been waiting for 30 minutes for the result of a fibrinogen level before the product was ordered. Indeed, even in the United States where cryoprecipitate is often provided in pre-pooled units (usually two doses/each dose a bag of multiple units of cryoprecipitate), studies have shown that cryoprecipitate is given 2.7 hours post trauma admission and after 8 units of red cells have already been administered.[13] We would argue that this is possibly too late into the course of a major hemorrhage. What if instead we had a fibrinogen product in the trauma room or the operating room that could be rapidly prepared as soon as the clinical team recognized the need for fibrinogen replacement? We can cut the order-to-needle time by 30 minutes with fibrinogen concentrate stored at the point of need. This is logistically possible for fibrinogen concentrate given that it can be stored at room temperature and be readily prepared for administration. This might make the difference between life and death in a patient with a massive hemorrhage, particularly a traumatically injured patient or a woman with a life-threatening postpartum hemorrhage.[14,15] In addition, it would be impossible to move cryoprecipitate into the pre-hospital phase of care or for that matter into a small rural hospital with infrequent use and a single combined hematology and blood bank technologist to manage all the laboratory needs of a massively bleeding patient.

To summarize, a transition from cryoprecipitate to fibrinogen concentrate is appropriate for logistical reasons, for differences in product attributes, and for recipient safety. The switch will be seen favorably by the hospital blood banks and blood suppliers alike. Let us put fibrinogen in the trauma rooms and the operating rooms to remove the 30-minute order-to-needle time. And let us make the correct decision regarding emerging pathogens—tens of thousands of patients will be infected by the time we realize we have another epidemic. We have the results of a definitive trial finding fibrinogen concentrates are non-inferior to cryoprecipitate in terms of hemostatic efficacy. The argument that we cannot switch because there may be hemostatic benefits to the impurities in cryoprecipitate is no longer valid. There is nothing now standing in the way of switching to a safer fibrinogen replacement product other than, arguably, costs to healthcare system, but we cannot be complacent on this front. There will likely be other emerging pathogens that will enter the blood system and if the models are correct, the human and financial costs will be staggering. For the sake of our patients we must implement pathogen-reduced fibrinogen concentrates and finally archive cryoprecipitate.

PRO CRYOPRECIPITATE: CRYOPRECIPITATE IS THE PREFERRED BLOOD PRODUCT FOR FIBRINOGEN REPLACEMENT IN THE BLEEDING PATIENT WITH ACQUIRED HYPOFIBRINOGENEMIA

In this section of our debate, we will attempt to convince you that cryoprecipitate is an important and necessary component for the management of hemorrhage in the presence of acquired hypofibrinogenemia. In this setting, physicians need a product like cryoprecipitate that addresses multiple deficiencies in hemostasis. In addition, many places in the world do not have the resources to manufacture or purchase fibrinogen concentrate and other blood derivatives. There are three parts to our argument for the use of cryoprecipitate over fibrinogen concentrates: 1) product superiority, 2) recipient safety, and (3) logistical advantages.

Product superiority

Cryoprecipitate can be considered superior to fibrinogen concentrate in two ways; first, the cost of manufacturing the product is much less than fibrinogen concentrate and second, the contents of cryoprecipitate address all phases of hemostasis.

The cost of blood product manufacturing is a major consideration for all countries. The process to pool, pathogen inactivate, and test is substantial for fibrinogen concentrate. A recent economic evaluation found that fibrinogen concentrate is more expensive than cryoprecipitate even after adjusting for cryoprecipitate wastage and a blood bank technologist's salary.[6] Low human development index countries and any country looking to contain costs may not be willing to pay for fibrinogen concentrate. Lack of availability of a fibrinogen product can be a safety concern for patients with hemorrhage because it may necessitate the use of additional unnecessary, non-specific blood products, such as plasma.

Cryoprecipitate contains fibrinogen, factor VIII, factor XIII, von Willebrand factor (VWF), and fibronectin. The beauty of cryoprecipitate is that it has the ability to improve all four stages of hemostasis (primary hemostasis, thrombin generation, fibrin polymerization and lysis). If you tried to do this with factor concentrates, you would need to give at least four different products. The VWF factor in cryoprecipitate has the potential to improve primary hemostasis. Takahashi published data showing that cryoprecipitate can enhance primary hemostasis via improved platelet aggregation.[16] The FVIII can improve thrombin generation. In fact, in a recent study Tanaka et al found that cryoprecipitate improves thrombin generation in the ROTEM INTEM clotting time better than fibrinogen concentrate in a dilutional coagulopathy model using samples from normal pregnant women.[17] It is well known that the fibrinogen in cryoprecipitate improves fibrin polymerization, this is its main use in the current time. Multiple studies have evaluated whether cryoprecipitate or

fibrinogen concentrate has superior efficacy for fibrinogen replacement, including two randomized controlled trials in cardiac surgery (one in adults[3] and one in pediatrics[18]) and a few observational studies.[19] These studies (excluding the FIBRES study) were summarized and analyzed in a recent systematic review comparing the efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients.[19] No study published to date has found a significant difference in efficacy. Finally, in the last stage of hemostasis, FXIII can help mitigate hyperfibrinolysis. Cushing et al demonstrated that cryoprecipitate reverses hyperfibrinolysis better than fibrinogen concentrate in an in vitro study.[20] In addition, cryoprecipitate contains fibronectin which is a regulator of hemostasis,[21] improves the innate immune response,[22] and promotes wound healing[23] (as does FXIII). Wang et al found that plasma fibronectin controls the diameter of fibrin fibers and promotes the stability of the hemostatic plug.[21]

Recipient safety

Recipient safety is a definite risk for the most common version of cryoprecipitate that is used today: a pooled product that is not pathogen reduced. This is an unacceptable, concerning risk as stated above. A pathogen reduced cryoprecipitate can be developed that is as effective as today's standard product.[24] Although cryoprecipitate and fibrinogen concentrates are pooled, plasma from more than 1000 donors are used for a lot of fibrinogen concentrate, whereas the pool for cryoprecipitate is made from only a few plasma donors. This could equate to a major difference in donor exposures and recipients infected for an emerging, unrecognized pathogen that is not susceptible to pathogen reduction techniques (e.g., a prion or non-encapsulated virus).

Logistical advantages of cryoprecipitate

Although the logistics related to the most commonly used cryoprecipitate products are significant, there are multiple opportunities to improve the product. First, in most transfusion services the pooling issue has already been resolved by the blood supplier (although this still requires manual pooling at the time of manufacture). It is ideal to receive a product into inventory that has been pre-pooled in a sterile manner into standard doses of multiple units, thus allowing the transfusion service to simply thaw and issue the product rather than having to physically and electronically pool it prior to issue. This can and should be addressed by all blood suppliers who offer cryoprecipitate. Second, the common problem of frequent wastage due to product expiration can be addressed by changing the shelf life of cryoprecipitate. Many studies have proven that the product is still effective for fibrinogen replacement after the current expiration time, and up to 35 days after thawing.[25–28] Fenderson et al. cultured eight cryoprecipitate units at 35 days after thawing and bacterial contamination was not observed in either the cold stored or room temperature stored cryoprecipitate.[25] Although Ramirez-Arcos et al. showed that bacteria can grow in cryoprecipitate stored at room temperature,[29] the technique used to manufacture and pool cryoprecipitate should be sterile, and subsequently the product undergoes a cryopreservation step, therefore making the likelihood of a contaminated product extremely low. An extension of the shelf life of cryoprecipitate after thawing would require regulatory and labeling changes, in addition to changes in transfusion medicine standards. A pathogen reduced cryoprecipitate product would further reduce this risk to an infinitesimal level. A third logistical disadvantage of cryoprecipitate, the delay in availability of the product at the time of hemorrhage, can also be addressed, and potentially this product can be available for infusion even sooner than fibrinogen concentrate. If the product is allowed a longer storage life as described above, it can be immediately available at room temperature in a liquid state and ready to infuse. This would actually be superior to fibrinogen concentrate which takes a minimum of 5 minutes to reconstitute (or up to 10 minutes for certain products and depending whether it is stored at room temperature or refrigerated temperatures).

To summarize, cryoprecipitate is advantageous over fibrinogen concentrate due to the fact that it is significantly less costly to manufacture, its components address all phases of hemostasis, and because a thawed room temperature pathogen reduced version of the product could be immediately available in large hospital centers for infusion in a hemorrhaging patient without any further manipulation or reconstitution. In smaller hospitals it would be harder to keep a pathogen reduced cryoprecipitate thawed at all times, so logistical delays would still occur in the rare occasions when fibrinogen supplementation was required.

CONCLUSION

Now that our objective arguments have been made for each product, we would like to state our overall opinions about the future of fibrinogen replacement. Undoubtedly, administering fibrinogen plays a critical role in acute hemorrhage management, and thus, timely treatment of hypofibrinogenemia should be ensured by all means. Notably, while clinicians who have access to fibrinogen concentrate are well aware and regularly in favor of the practical advantages of administering this potent and easy to reconstitute blood product, current literature has not yet revealed its true superiority over cryoprecipitate. It can be speculated that this could be due to a dearth of larger randomized trials, however, it should be noted that there is a striking difference between the two fibrinogen containing products: while fibrinogen concentrate offers a highly purified single factor concentrate, cryoprecipitate comes with a spectrum of other coagulation factors which may further enhance (additional procoagulant effect) or even disturb (prothrombotic risk) the overall hemostatic potential by

inadequate or repetitive usage. Unfortunately, purified coagulation factors come with the "price" of increased costs. Whether this can be counterbalanced or justified by its improved safety profile and the costs avoided by preventing transfusion-transmitted infections needs to be confirmed by thoroughly analyzing hemovigilance data and mathematical models of future emerging pathogens. The faster availability of fibrinogen concentrate may tip the scale towards more effective use during the treatment of life-threatening hemorrhage. Regardless of which tool you have in your armory for the treatment of acute hemorrhage, the importance of the targeted treatment of acquired hypofibrinogenemia with a concentrated fibrinogen product (either cryoprecipitate or fibrinogen concentrate) cannot be underestimated.

SOURCE OF SUPPORT

None.

CONFLICTS OF INTEREST

MC is a consultant for Cerus Corporation and Octapharma. TH is a consultant for Octapharma and a member of the Speaker's Bureau for Octapharma and Instrumentation Laboratories. KK is in part supported by a merit award from the Department of Anesthesia, University of Toronto, and has received research support and honoraria for speaking engagements from Octapharma. JC has received research support from CSL Behring, Octapharma, and Canadian Blood Services.

REFERENCES

1. Klein HG, Anderson D, Bernardi MJ, et al. Pathogen inactivation: making decisions about new technologies. Report of a consensus conference. Transfusion 2007;47:2338-47.
2. Atreya C, Glynn S, Busch M, et al. Proceedings of the food and drug administration public workshop on pathogen reduction technologies for blood safety 2018 (Commentary, p. 3026). Transfusion 2019;59:3002-25.
3. Callum J, Farkouh ME, Scales DC, et al. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery: the FIBRES randomized clinical trial. JAMA 2019:1-11.
4. Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. Transfus Med Rev 2009;23:177-88.
5. Cushing MM, Haas T. Fibrinogen concentrate for perioperative bleeding: what can we learn from the clinical trials? Transfusion 2019;59:3295-3297.
6. Okerberg CK, Williams LA 3rd, Kilgore ML, et al. Cryoprecipitate AHF vs. fibrinogen concentrates for fibrinogen replacement in acquired bleeding patients - an economic evaluation. Vox Sang 2016;111:292-8.
7. Kleinman S, Cameron C, Custer B, et al. Modeling the risk of an emerging pathogen entering the Canadian blood supply. Transfusion 2010;50:2592-606.
8. Foglieni B, Candotti D, Guarnori I, et al. A cluster of human immunodeficiency virus Type 1 recombinant form escaping detection by commercial genomic amplification assays. Transfusion 2011;51:719-30.
9. Roy A, Stanford S, Nunn S, et al. Efficacy of fibrinogen concentrate in major abdominal surgery - a prospective, randomized, controlled study in cytoreductive surgery for pseudomyxoma peritonei. In: J Thromb Haemost; 2019. [Epub ahead of print].
10. Heddle NM, Arnold DM, Acker JP, et al. Red blood cell processing methods and in-hospital mortality: a transfusion registry cohort study. Lancet Haematol 2016;3:e246-54.
11. Jordan A, Chen D, Yi QL, et al. Assessing the influence of component processing and donor characteristics on quality of red cell concentrates using quality control data. Vox Sang 2016;111:8-15.
12. Dunbar NM, Olson NJ, Szczepiorkowski ZM, et al. Blood component transfusion and wastage rates in the setting of massive transfusion in three regional trauma centers. Transfusion 2017;57:45-52.
13. Holcomb JB, Fox EE, Zhang X, et al. Cryoprecipitate use in the PROMMTT study. J Trauma Acute Care Surg 2013;75:S31-9.
14. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007;5:266-73.
15. Leal-Noval SR, Casado M, Arellano-Orden V, et al. Administration of fibrinogen concentrate for refractory bleeding in massively transfused, non-trauma patients with coagulopathy: a retrospective study with comparator group. BMC Anesthesiol 2014;14:109.
16. Takahashi H, Okada K, Abe S, et al. Platelet aggregation induced by cryoprecipitate infusion in platelet-type von Willebrand's disease. Thromb Res 1987;46:255-62.
17. Tanaka KA, Bharadwaj S, Hasan S, et al. Elevated fibrinogen, von Willebrand factor, and Factor VIII confer resistance to dilutional coagulopathy and activated protein C in normal pregnant women. Br J Anaesth 2019;122:751-9.
18. Galas FR, de Almeida JP, Fukushima JT, et al. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. J Thorac Cardiovasc Surg 2014;148:1647-55.
19. Jensen NH, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. Acta Anaesthesiol Scand 2016;60:1033-42.
20. Cushing MM, Fitzgerald MM, Harris RM, et al. Influence of cryoprecipitate, Factor XIII, and fibrinogen concentrate on hyperfibrinolysis. Transfusion 2017;57:2502-10.
21. Wang Y, Reheman A, Spring CM, et al. Plasma fibronectin supports hemostasis and regulates thrombosis. J Clin Invest 2014;124:4281-93.
22. Fei D, Meng X, Yu W, et al. Fibronectin (FN) cooperated with TLR2/TLR4 receptor to promote innate immune responses of macrophages via binding to integrin beta1. Virulence 2018;9:1588-600.
23. Lenselink EA. Role of fibronectin in normal wound healing. Int Wound J 2015;12:313-6.

24. Cushing MM, Asmis LM, Harris RM, et al. Efficacy of a new pathogen-reduced cryoprecipitate stored 5 days after thawing to correct dilutional coagulopathy in vitro. Transfusion 2019;59:1818-26.
25. Fenderson JL, Meledeo MA, Rendo MJ, et al. Hemostatic characteristics of thawed, pooled cryoprecipitate stored for 35 days at refrigerated and room temperatures. Transfusion 2019;59:1560-7.
26. Lokhandwala PM, O'Neal A, Patel EU, et al. Hemostatic profile and safety of pooled cryoprecipitate up to 120 hours after thawing. Transfusion 2018;58:1126-31.
27. Soundar EP, Reyes M, Korte L, et al. Characteristics of thawed pooled cryoprecipitate stored at refrigerated temperature for 24 hours. Blood Transfus 2018;16:443-6.
28. Green L, Backholer L, Wiltshire M, et al. The hemostatic properties of thawed pooled cryoprecipitate up to 72 hours. Transfusion 2016;56:1356-61.
29. Ramirez-Arcos S, Jenkins C, Sheffield WP. Bacteria can proliferate in thawed cryoprecipitate stored at room temperature for longer than 4 h. Vox Sang 2017;112:477-9.