

Use of Cryoprecipitate in Newborn Infants

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ABSTRACT

Cryoprecipitate is a transfusion blood product derived from fresh-frozen plasma (FFP), comprised mainly of the insoluble precipitate that gravitates to the bottom of the container when plasma is thawed and refrozen. It is highly enriched in coagulation factors I (fibrinogen), VIII, and XIII; von Willebrand factor (vWF); and fibronectin. In this article, we have reviewed currently available information on the preparation, properties, and clinical importance of cryoprecipitate in treating critically ill neonates. We have searched extensively in the databases PubMed, Embase, and Scopus after short-listing keywords to describe the current relevance of cryoprecipitate.

Keywords: Cryoprecipitate, Cryoprecipitated antihemophilic factor, Factor I, Factor VIII, Factor XII, Fibrinogen, Newborn neonate infant, Transfusion product.

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HIGHLIGHTS

- Cryoprecipitate is a transfusion product comprised of the insoluble precipitate that gravitates to the bottom of the container when fresh frozen plasma is thawed and refrozen. It contains physiologically relevant amounts of factors I (fibrinogen), VIII, XIII, vWF, and fibronectin.
- Cryoprecipitate is typically administered in a dose of 1 unit (40 mL) per 10 kg of body weight; this may raise the fibrinogen level by 50 mg/dL. In most neonates, the administration of 5–10 mL/kg is sufficient.
- For inherited coagulopathies such as hemophilia A, deficiency of factor XIII, hypofibrinogenemia, and vWD, cryoprecipitate transfusions are no longer recommended unless specific factor replacement products are not available.
- For treatment of acquired fibrinogen deficiency due to disseminated intravascular coagulation (DIC), severe liver failure, and consumptive coagulopathy, cryoprecipitate is primarily used in the presence of bleeding and fibrinogen levels less than 1 gm/L.

INTRODUCTION

Cryoprecipitate (cryo; cryoprecipitated antihemophilic factor) is a transfusion product derived from plasma, enriched in factors I (fibrinogen), VIII, XIII, vWF, and fibronectin.^{1–5} It was historically labeled as the cryoprecipitated antihemophilic factor in view of the high concentrations of factor VIII and its hemostatic efficiency in patients with hemophilia A.^{6–8}

Guidelines for the use of cryoprecipitate in neonatal medicine are limited to a few conditions. In the setting of inherited disorders of hemostasis, cryoprecipitate should be used as replacement therapy only if specific factor concentrate is not available while in the setting of acquired hypofibrinogenemia during DIC or liver failure, its use is considered standard therapy despite the lack of evidence.⁹

In this article, we aimed to review current information on the preparation, properties, and clinical importance of cryoprecipitate in critically ill neonates. We have extensively searched the databases PubMed, Embase, and Scopus after short-listing the keywords to describe the current relevance of cryoprecipitate. Furthermore, we reviewed the last 10 years of practice in a tertiary neonatal

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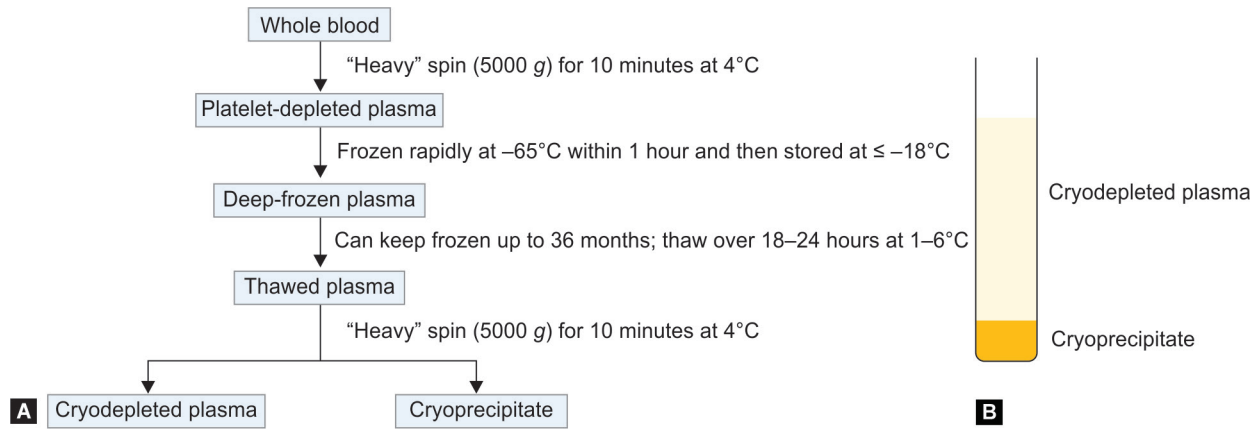
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unit in Italy with the aim to describe the common clinical use of cryoprecipitate in critically ill neonates.

PREPARATION AND STORAGE OF CRYOPRECIPITATE

Cryoprecipitate is prepared from whole blood (Flowchart 1).¹⁰ First, freshly isolated whole blood of a specific ABO group is processed to isolate platelet-depleted plasma; it is subjected to a "heavy" spin (5000 g) for 10 minutes at 4°C in a refrigerated centrifuge.^{11–14} This plasma supernatant is frozen at –65°C ideally within 1 hour, but possibly up until 8 hours after isolation, and is then stored at or below –18°C.¹ The duration prior to its being frozen is important because many coagulation factors get degraded over time. Next, this FFP is used to prepare cryoprecipitate. The FFP is thawed either over 18–24 hours at 1–6°C, or more rapidly in a circulating water bath.¹⁵ A slushy cryoprecipitate layer seen at the bottom of the bag has a thick, white to semi-opaque appearance, and can be separated

Flowchart 1A and B: (A) Flowchart explaining whole blood is processed to prepare cryoprecipitate in multiple steps; (B) After processing, two distinct layers of cryoprecipitate and cryosupernatant (cryodepleted plasma) can be seen



using another “heavy” spin.^{16–19} After complete processing, the cryoprecipitate is deep frozen until needed for clinical use.²⁰ Most of the supernatant, except for about 10–15 mL, is removed by gravity drainage or a plasma expessor.²¹ This clear layer of plasma above this precipitate is known as the cryosupernatant or cryodepleted plasma.^{10,22–26}

The American Association of Blood Banks (AABB) recommends that frozen cryoprecipitate should be thawed prior to use in a protective plastic overwrap in a water bath at 30–37°C.^{27,28} Once thawed, cryoprecipitate can be stored at 20–24°C for up to 4–6 hours.^{29–32} We typically pool thawed preparations from 5 donors before use, and use these units within 4 hours. Fibrinogen and factor VIII in cryoprecipitate are labile proteins and are lost over time.^{4,33} Cryoprecipitate unit prepared from a standard 450–500 mL whole blood anticoagulated with citrate–phosphate–dextrose–adenine should contain at least 150 mg of fibrinogen and a minimum of 80 international units (IU) of factor VIII.^{4,34,35} This contains approximately 30–70% of factor VIII/vWF and fibrinogen content of the original preparation.^{3,36,37}

Cryoprecipitate can also be prepared from plasma frozen within 24 hours of collection [frozen plasma–24 hours (FP24)].¹ It is usually prepared by pooling plasma from multiple donors rather than a single unit. Pooling is performed either before freezing by the central blood bank or after thawing by licensed centers. The freezing and thawing of plasma generate platelet membrane microparticles, and these are further concentrated by cryoprecipitation; the microparticle concentration of cryoprecipitate is 250-fold higher than the source plasma.³⁸ These microparticles contain glycoproteins that interact with fibrinogen, vWF, and platelets, and these interactions may be enhanced by cryoprecipitation.¹ The role of these microparticles in hemostasis, vascular function, inflammation, or alloimmunoreactivity is unknown.³⁹ The effect of processing and freezing of cryoprecipitate on these microparticles is also not known. Cryoprecipitates produced by pathogen-reduced apheresis using amotosalen and ultraviolet light A can be useful.⁴⁰ Amotosalen hydrochloride (HCl) is a photoactive psoralen compound with a characteristic three-ring structure.⁴¹ It blocks the proliferation of pathogens by non-specific inhibition of DNA and RNA replication in the presence of ultraviolet A, and it can be reliably removed to trace levels prior to transfusions.⁴²

Cryoprecipitate can be stored for a maximum of 36 months.⁴³ After thawing, the product should be visually examined

to ensure that there are no insoluble fractions and that the container is intact.^{44,45} The cryoprecipitate should be used immediately, ideally within 4 hours of its being thawed and received from the blood bank, and should never be refrozen.^{27,46–48} The shelf life of thawed cryoprecipitate is short due to the loss of clotting factor activity, particularly that of factor VIII.

A single unit of cryoprecipitate received from the blood bank is made by thawing and pooling material from several donors.⁴⁹ The British Committee for Standards in Haematology recommends that cryoprecipitate should be administered in doses of 5–10 mL/kg, using higher volumes in bleeding neonates. The recipients should be monitored for clinical outcome and fibrinogen levels.⁵⁰ One unit (40 mL) of cryoprecipitate per 10-kg body weight may raise the plasma fibrinogen concentrations by up to 50 mg/dL in the absence of continued consumption or massive bleeding.⁵¹ Although cryoprecipitate transfusions do not always need to be ABO compatible due to the small volumes of plasma in the units, neonates should still be given ABO-compatible units whenever possible due to their small body volumes.⁵²

CLINICAL USE

Cryoprecipitate was routinely administered from the 1970s to the 1990s to treat hemophilia A and various factor deficiencies. Today, due to the availability of recombinant or highly purified virus-inactivated plasma-derived concentrates the use of cryoprecipitate is no longer considered the first-choice treatment for inherited coagulopathies such as hemophilia A, deficiency of factor XIII, hypofibrinogenemia, and vWD.⁵³ Furthermore, clinical guidelines have recommended against cryoprecipitate for these conditions unless specific factor replacement products are not available. The preference for specific factors concentrates is because of less frequent transfusion reactions, transfusion-related acute lung injury, and the risk of infections.⁵³ In neonates, cryoprecipitate is administered primarily to correct acquired fibrinogen deficiency such as in DIC, liver failure and consumptive hypofibrinogenemia as might be seen in infants with multiple thromboses.

Over the years, increasing experience with viscoelastic tests in neonates has enhanced our confidence in the management of acquired coagulopathies.⁵⁴ Viscoelastic tests of coagulation such

as thromboelastography and rotational thromboelastometry analyze the viscoelastic properties of the clot and evaluate the entire hemostatic process from initial formation of the clot to the polymerization of fibrin.^{55,56} These tests can help measure the availability of functional fibrinogen (Fig. 1).⁵⁷

To determine the need for cryoprecipitate transfusions in level III neonatal intensive care unit, we reviewed data from the Children's Hospital of Brescia from the last 10 years. Nineteen infants received 26 cryoprecipitate transfusions for hypofibrinogenemia (Table 1). The main cause of hypofibrinogenemia was DIC in 16 cases (84%) secondary to severe infections, Necrotizing enterocolitis (NEC), birth asphyxia, and congenital sacrococcygeal teratoma. Three cases (16%) of liver failure received cryoprecipitate for hypofibrinogenemia. Prior to transfusion, the median (interquartile range) level of fibrinogen was 77 (35–94) mg/dL.

USE OF CRYOPRECIPITATE IN INHERITED COAGULATION DISORDERS

Hereditary fibrinogen abnormalities are rare bleeding abnormalities and can be divided into types I and II disorders. Type I disorders, including afibrinogenemia and hypofibrinogenemia, are quantitative fibrinogen deficiencies. Type II disorders affect the structure/function of circulating fibrinogen.⁵⁸ These diseases result from a variety of inherited genetic defects.⁵⁹ Most patients are asymptomatic, although some may have bleeding from the umbilical cord, mucosal surfaces, and intracerebral or intra-abdominal bleeding.⁵⁸ Tests show prolonged PT, Partial thromboplastin time (PTT), bleeding time and very low fibrinogen levels.³⁶ These clotting derangements may present in the neonatal period due to trauma of delivery. Fibrinogen concentrates are emerging as an important, safe option as a replacement therapy in congenital fibrinogen disorders. In addition, more accurate dosing can be achieved with fibrinogen concentrates because their potency is known, unlike FFP or cryoprecipitates. However, these products are still useful when fibrinogen concentrates are not available.⁵⁸

von Willebrand disease is an inherited bleeding disorder that manifests clinically with bleeding in approximately 1:10,000 individuals. It is caused by deficiency and/or defect in vWF.⁶⁰ The most common symptoms are mucocutaneous bleeding, hematomas and bleeding after trauma or surgery.⁶¹ Cryoprecipitate transfusions containing vWF are administered in patients who do not respond to desmopressin or for patients with type II or III vWD for treating bleeding episodes and for surgical procedures.^{62–64} It should be restricted to emergency therapy where factor VIII/vWF concentrates are not immediately available and bleeding is sufficiently severe to warrant the risks associated with cryoprecipitate.^{3,4,65} Therefore, it is strictly used as a second line therapy, only when desmopressin is not available.

Hereditary deficiency of factor XIII is an extremely rare condition; the Canadian hemophilia registry identified only 41 cases in 2006.⁶⁶ Compared to other factors, factor XIII is more stable with a longer half-life of 9–10 days.^{3,4,67} Umbilical bleeding is a frequently-seen finding in neonates, occurring in nearly 80% of cases. Intracranial hemorrhage has been reported in 25–30% cases and is the main cause of death or disability in these patients. Because of the rarity of factor XIII deficiency, specific factor concentrate is usually not readily available in emergent situation, and hence cryoprecipitate can be a useful remedy.^{3,4,68} It can be administered in a dose of 1 bag per 10–20 kg every 3–4 weeks.^{3,8}

USE OF CRYOPRECIPITATE IN ACQUIRED COAGULATION DISORDERS

Disseminated intravascular coagulation is an acquired, life-threatening condition that can occur in infants with conditions such as sepsis, respiratory distress syndrome, acidosis, NEC, birth asphyxia, and congenital sacrococcygeal teratoma.^{37,69–71} These disorders are marked by systemic activation of anticoagulation pathways. The management of DIC includes identification and treatment of the underlying condition and restoration of the hemostasis by transfusion of platelets, FFP, and cryoprecipitate. Cryoprecipitate has been used at a dose of 5–10 mL/kg in infants

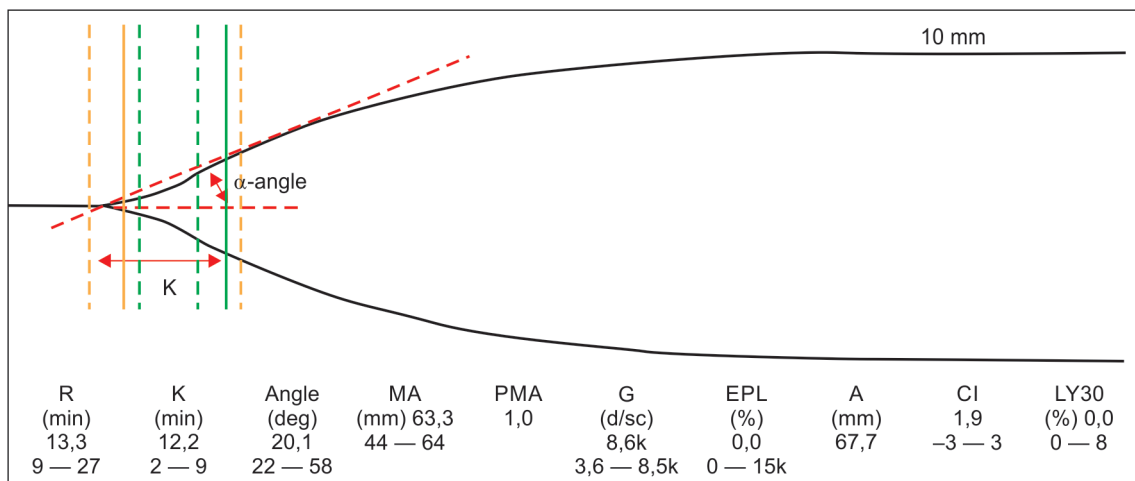


Fig. 1: Graphical representation of a thromboelastography test showing a prolonged K-time (clot kinetics) and a decreased α -angle (rate of clot formation) suggestive of hypofibrinogenemia. All labels are shown in deep red. K is the time taken to achieve a certain level of clot strength (amplitude of 20 mm); α -angle (degrees) measures speed at which fibrin build up and cross-linking takes place, rate of clot formation. R, reaction time; MA, maximum amplitude; PMA, projected MA; G, gear (shear elastic clot strength); EPL, estimated percentage of lysis; A, amplitude (at the latest time point); CI, coagulation index; LY, fibrinolysis

Table 1: Cases of hypofibrinogenemia receiving cryoprecipitate transfusions

Case	Year	GA (weeks)	BW (gm)	Diagnosis	Setting	Transfusion (n)	Other complications
1	2012	40	3,350	Galactosemia	Liver failure	1	
2	2012	23	378	Late-onset sepsis	DIC	2	
3	2012	29	1,390	Early-onset sepsis	DIC	3	
4	2013	24	650	Late-onset sepsis	DIC	1	
5	2013	28	700	Late-onset sepsis	DIC	1	
6	2013	30	885	Necrotizing enterocolitis	DIC	2	
7	2014	27	890	Necrotizing enterocolitis	DIC	1	
8	2014	33	4,280	Sacroccygeal teratoma	DIC	1	
9	2014	37	1,920	Birth asphyxia	DIC	1	
10	2014	33	1,650	Late-onset sepsis	DIC	1	Thrombosis
11	2016	27	439	Late-onset sepsis	DIC	2	
12	2016	26	890	Birth asphyxia	DIC	1	
13	2017	38	2,950	Late-onset sepsis	DIC	1	Thrombosis
14	2018	24	800	Late-onset sepsis	DIC	1	Thrombosis
15	2020	31	1,801	Pneumonia	DIC	1	
16	2020	39	3,130	Mitochondrial disease	Liver failure	1	
17	2020	27	658	Early-onset sepsis	DIC	1	
18	2022	30	1,350	UVC malposition	Liver failure	2	
19	2022	32	1,470	Necrotizing enterocolitis	DIC	2	

BW, birth weight; DIC, disseminated intravascular coagulation; GA, gestational age; UVC, umbilical venous catheter

with DIC and active bleeding if the fibrinogen values fall below 1 gm/L.⁵⁰ The British Committee for Standards in Haematology, Blood Transfusion Task Force published guidelines for the use of cryoprecipitate in 2004,²⁴ and supported the consideration of cryoprecipitate as a therapeutic modality at fibrinogen values below 1 gm/L in infants with active bleeding. However, admittedly, even though all guidelines for cryoprecipitate administration reiterate a therapeutic threshold of fibrinogen levels 1 gm/L, this cutoff is not based on strong clinical evidence.⁷² The thresholds for supplementation may have to be tailored based on the gestational and postnatal age of the patient, severity of illness, and the risk of mortality.⁷³

Sacroccygeal teratomas are the most common congenital tumors associated with hemorrhagic complications.^{74,75} The coagulopathy that develops in these infants may be due to the consumption of clotting factors as a result of bleeding *in utero* or during labor and delivery. The etiology of the clotting abnormalities is multifactorial and leading to DIC.⁷⁵ The tumor may also have endothelial abnormalities and the microvascular disruptions during labor and delivery may trigger DIC. Trauma to the teratomas during delivery may release tissue thromboplastins into the bloodstream, resulting in activation of the coagulation cascade.⁷⁵ The blood loss is often difficult to assess as there might be concealed losses inside the necrotic tissues inside the tumors. In one study, the surgeons estimated blood losses of around 300 mL. The average transfusion volumes included packed red blood cell transfusions of 320 mL; FFP, 43 mL; platelets, 40 mL; cryoprecipitate, 20 mL; and crystalloids 90 mL.⁷⁶

Many infants who have undergone major surgical procedures or have sustained trauma develop large hemorrhages. These

hemorrhages can accentuate fibrinolysis and induce hypo-/dysfibrinogenemia.⁷⁷⁻⁷⁹ Platelets and cryoprecipitate must be considered as therapeutic options if active bleeding persists after initial resuscitation as fibrinogen levels can drop drastically in these patients.⁸⁰ Cryoprecipitate is usually given in a dose of 10 mL/kg. Tama et al.⁸¹ reviewed Pediatric Trauma Quality Improvement Program data and evaluated the mortality benefit from early administration of cryoprecipitate. They showed that patients who received cryoprecipitate had lower 24-hour mortality. The benefits were even more prominent in infants and children who needed transfusions more than 100 mL/kg.

Many infants undergoing surgical procedures such as cardiac surgery with cardiopulmonary bypass (CPB) are at risk of life-threatening hemorrhages.^{82,83} Usually, pre-operative hemostasis is optimized using steps such as adequate vitamin K replacement. Pre-operative prophylactic transfusion with FFP or cryoprecipitate is not indicated for patients with minor coagulation abnormalities, particularly in those who have been anticoagulated prior to CPB. However, if there is post-operative bleeding and APTT is prolonged it is important to ensure that heparin has been adequately reversed. CPB in neonates may cause marked reduction in clotting factors including fibrinogen, due to hemodilution, loss from the circuit and consumption.³⁶ A fibrinogen level of 1.5 gm/L is aimed for, and used as a transfusion threshold for cryoprecipitate.³⁶ There have been some studies to compare the efficacy of cryoprecipitate and fibrinogen concentrates, but the number of subjects has not been statistically adequate.⁸⁴

Extracorporeal membrane oxygenation (ECMO) is increasingly used in critically ill infants to provide life-saving cardiopulmonary

support. As ECMO circuits expose circulating blood to artificial and non-endothelial surfaces, there is fibrinogen adsorption, contact pathway activation, coagulation activation, thrombin generation, and fibrinolysis. Many infants with these hemorrhagic complications are treated with FFP and/or cryoprecipitate.^{85–89} Neonates undergoing treatment with ECMO have had a higher frequency of intracranial hemorrhage when they had low fibrinogen levels.^{90,91} The ELSO guidelines advise for transfusion of plasma or cryoprecipitate to maintain fibrinogen levels above 150 mg/dL.⁹²

Severe liver disease in newborns is relatively rare but can occur due to viral infections, hereditary metabolic diseases, neoplasia, and vascular problems.⁹³ Liver diseases are frequently associated with low fibrinogen levels and can be treated with cryoprecipitate.⁹⁴ The evidence of benefit still needs to be proven as the sample sizes in published studies are small.⁹⁵ Cryoprecipitate may sometimes also be inadequate because of the deficiency of multiple coagulation factors.⁹⁴

Some rare but potentially life-threatening causes of acquired hypofibrinogenemia include purpura fulminans due to congenital deficiency of protein C or S. Other cases may have the Kasabach–Merit phenomenon, an acute consumptive coagulopathy that is specifically associated with vascular tumors.⁹⁶ These infants with rapidly growing tumors develop platelet sequestration with consequent thrombocytopenia and fibrinogen consumption.^{97,98} Cryoprecipitate can be used if fibrinogen levels are <100 mg/dL, particularly if there is clinically-evident bleeding.^{97,99}

ADVERSE EFFECTS

Cryoprecipitate can have adverse effects such as infections, transfusion-associated circulatory overload, transfusion-related acute lung injury, and other transfusion reactions.¹⁰⁰ There have also been reports implicating cryoprecipitate as a cause of anaphylactic shock, intravascular hemolysis, and biliary complications.¹⁰¹ The risk of infections, such as with bacteria, human immunodeficiency virus, and hepatitis viruses B and C, is similar to other transfusion units.^{102–111} The risk of infections with cryoprecipitate might be higher than with fibrinogen concentrate as the latter involves more stringent steps including pasteurization, adsorption, and precipitation, which remove or inactivate a wide range of enveloped and non-enveloped viruses.¹¹² The risk of acquiring HIV from contaminated blood varies widely among countries and varies with the background incidence rate of HIV among donors, quality of screening assays, access to laboratories, the total number of transfusions, or exposures to the recipient.¹¹² The risk of transmission may be higher in developing countries as the cryoprecipitates are made from locally supplied blood and as compared to developed countries where the product is virus inactivated.¹¹² Cryoprecipitate is less likely to cause transfusion-related volume overload as compared to FFP. It has also a lower risk of causing hemolytic transfusion reaction than the plasma and this risk can be further reduced if ABO compatibility can be assured.

CONTRAINDICATIONS

Cryoprecipitate may not be adequate as replacement therapy for isolated factor deficiencies of fibrinogen, factors VIII and XIII, or vWF if the appropriate factor concentrates are available.^{3,113} It cannot also be used for replacement therapy for other factors.¹¹⁴ FDA has approved the use of recombinant coagulation factor

therapy as individual factor concentrates are now available for replacement therapies for hemophilia, factor XIII deficiency, hypofibrinogenemia, and vWD.¹¹⁵ Moreover, clinical guidelines have recommended against cryoprecipitate for these conditions unless specific factor replacement products are unavailable because of fewer adverse events.^{114,116} It has been withdrawn from many European countries because of safety concerns such as the transmission of pathogens. Nevertheless, cryoprecipitate is still available for hemostatic therapy in several countries, including the USA and Canada.¹ Although fibrinogen concentrate is licensed in the USA for use for congenital deficiencies, cryoprecipitate is still used to treat acquired fibrinogen deficiencies.¹¹⁴ Considering the variable need for cryoprecipitates versus other blood products, one possible solution may be the development of computational monitoring systems for the utilization of blood products.¹¹⁷

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