What studies show for extended-life cryoprecipitate

Amy Carpenter

August 2024–Extended-life cryoprecipitate has several pluses: longer shelf life, preserved fibrinogen function, and low risk of bacterial contamination, among others.

“The big con is cost,” said Jay Hudgins, DO, MS, director of hemostasis and thrombosis, Department of Pathology and Laboratory Medicine, Nationwide Children’s Hospital, Columbus, Ohio.

“Pathogen-reduced cryoprecipitate is often about two times the overall cost of standard cryoprecipitate,” putting it out of reach for many hospitals, he said. But its potential to reduce wastage and for better inventory management during a shortage are other factors to weigh.

Dr. Hudgins reported what he and colleagues at Los Angeles General Medical Center (before his move to Nationwide) found when they sifted through the studies on extended-life cryoprecipitate, during a time of shortage. He spoke at the CAP23 meeting last fall in a session that also covered use of low titer O whole blood and cold-stored platelets (see the July issue, https://bit.ly/CT_0724-LTOWB).

Dr. Hudgins

Cryoprecipitate antihemophilic factor is manufactured from fresh frozen plasma and enriched with five plasma proteins: four coagulant factors (fibrinogen, factor VIII, von Willebrand factor, and factor XIII) and fibronectin, which aids tissue recovery and repair. Today, “we primarily use it for fibrinogen replacement” in cases of disseminated intravascular coagulation or extracorporeal circuit hypofibrinogenemia, Dr. Hudgins said. He uses it in patients who have uremic bleeding and are not good candidates for platelet transfusion and in patients who have massive transfusion. It is used also in patients with cirrhosis.

Improper use leads to cryoprecipitate wastage, and in Dr. Hudgins’ experience, “people ordering it in error” can be a problem, he said. An unknown fibrinogen status preoperatively or postoperatively in anesthesia or ICU settings will lead to improper use or request, as does the belief by those who want to reverse an anticoagulant that cryoprecipitate is a concentrated plasma. Treating an elevated international normalized ratio is another misuse. All are “potential issues for utilization monitoring,” Dr. Hudgins said.

Transfusion of cryoprecipitate antihemophilic factor units rose 11.3 percent from 2017 to 2019 and six percent between 2019 and 2021, according to 2019 and 2021 National Blood Collection and Utilization Survey data. “So we’ve seen about a 17 percent increase in the use of cryoprecipitate from 2017 to 2021,” Dr. Hudgins said. “I don’t think it will be any less in the next iteration.”

Overall blood product wastage rose by 12.1 percent between 2017 and 2019, and cryoprecipitate unit wastage rose about 7.5 percent. The mean dollar amount paid for cryoprecipitated AHF in 2019 was about $55 per unit ($275 per pool), and the range varied by up to $70 per unit.

The 2021 data revealed a cost increase for most blood products between 2019 and 2021. Wastage numbers were not broken down in the 2021 data by plasma, platelets, and cryoprecipitate.

The reasons for cryoprecipitate wastage are common: the limited use cases, short expiration times, unusual

storage conditions, and inappropriate ordering practices.

During the COVID-19 pandemic, Dr. Hudgins said, “plasma derivatives such as cryoprecipitate were sacrificed in lieu of COVID convalescent plasma manufacturing.”

The protracted shortage led to increased off-label use of fibrinogen concentrate, triage for all uses of cryoprecipitate AHF, and rationing of blood products to extend inventory.

Cryoprecipitate mitigation became a priority at Los Angeles General Medical Center, Dr. Hudgins said. “We wanted to make sure we had this blood product to give to our trauma and cirrhotic patients in the hospital.”

Thus the focus on extended-life cryoprecipitate and its safety, potency, and purity. Potential bacterial contamination after thaw was the primary impetus for all three pillars, he said, “but for the pathogen reduction component, we can also implement elements for viral infection.”

Whether refrigerated or room temperature components were better in this instance was a question, Dr. Hudgins said, because “we’ve seen with cold-storage platelets and for whole blood that the storage of these components may affect their coagulation activity.” Duration was another question. Extended-life cryoprecipitate has been studied from about 24 hours to more than 120 hours. “But when we think about pathogen-reduced cryoprecipitate products, 120 hours is going to be the limit” to consider.

As to potency, they looked at the function of the coagulation factors contained within, with most studies having evaluated fibrinogen and factor VIII and von Willebrand factor activity, he said. “The rarity of issues with factor XIII makes it less likely to be studied.” The purity pillar was centered on the effect of pathogen reduction technology.

Dr. Hudgins and colleagues dug into the published data.

Soundar, et al., studied 10 units of pooled, thawed cryoprecipitate stored at room temperature for six hours and then at 1°–6°C for 18 hours after thawing (Soundar EP, et al. *Blood Transfus*. 2018;16[5]:443–446). The pools were examined at zero, six, and 24 hours (aerobic and anaerobic bacterial cultures) for fibrinogen concentration, factor VIII and vWF activity, and sterility.

The mean fibrinogen concentration and vWF activity were similar at each time point, the authors reported, but factor VIII activity decreased significantly over the storage period. “But because that’s not the primary reason to administer cryoprecipitate,” Dr. Hudgins said, “it’s less of an issue for this component as we’re moving forward. And bacterial growth was not detected in any of the aliquots generated from this particular study.”

The study’s time frame was limited, he noted. The larger issue: “They’re only looking at the refrigerated component, so can we get something that will look at ambient temperatures?”

Lokhandwala, et al., studied the hemostatic profile and safety of pooled cryoprecipitate up to 120 hours after thawing (Lokhandwala PM, et al. *Transfusion*. 2018;58[5]:1126–1131). Thirty cryoprecipitate pools—20 type A and 10 type O—held at ambient temperatures were sampled for coagulation factor activity at zero, four, eight, 24, 48, and 120 hours post-thaw. They were cultured at zero and 120 hours for sterility. They pulled out an additional 60 units to culture at 72 hours. “They were doing so much sampling, there was a concern they might be introducing some error,” Dr. Hudgins said.

After 120 hours, the authors found no decline in fibrinogen levels or vWF activity. The authors write, “Of the pools tested, 75% of products (15 of 20) met the AABB required standard for FVIII of 80 IU/unit at the time of thawing, which decreased to 60% at 120 hours. All group A cryoprecipitate pools met the AABB required standard for FVIII of 80 IU/unit at 0 hours, declining to 80% of cryoprecipitate pools meeting the standard at 120 hours.” Fifty percent of the group O cryoprecipitate pools met the standard requirement of 80 IU/mL at zero hours; at 120 hours it decreased to 40 percent.

Said Dr. Hudgins: “The O plasma typically has a lower concentration of von Willebrand factor in it so there is a lower concentration of factor VIII overall, which contributed to this. And von Willebrand factor was basically the same throughout the entirety of this component. So our primary use case of fibrinogen replacement is very good. Any use cases around factor VIII, as long as it’s a non-O component, probably will be okay. And if you’re also using this as an emergency relief issue for von Willebrand disease, it may be beneficial.”

One of 20 pools grew bacteria after 120 hours. The 60 additional units sampled at 72 hours had no growth.

Fenderson, et al., evaluated the hemostatic characteristics of thawed, pooled cryoprecipitate for 35 days to assess the feasibility of increasing shelf life, as well as the hemostatic function of cold-stored and room-temperature–stored cryoprecipitate (Fenderson JL, et al. *Transfusion*. 2019;59(S2):1560–1567).

They sampled eight thawed cryoprecipitate pools (four type A, four type O) stored at 1°–6°C and at 21°–24°C at four, seven, and 24 hours and weekly for 35 days. No significant differences were observed in the hemostatic properties of the type A and type O cryoprecipitate samples, and therefore they were combined for data analysis.

In this study, Dr. Hudgins said, “you did see a decrease in fibrinogen activity at about 21 days for the room temperature components,” whereas for the refrigerated components there was no significant difference between time zero and 35 days. The fibrinogen concentration of refrigerated and room temperature cryoprecipitate didn’t differ significantly at any time point.

FVIII activity declined rapidly, with a significant drop by four hours in room temperature and 24 hours in cold-stored samples, and vWF activity declined gradually and was significantly diminished at 14 days in the room temperature and at 21 days in the refrigerated samples.

In concurrent studies, thrombin generation parameters showed that lag time declined in cold-stored samples, significantly only on day three, while endogenous thrombin potential and peak thrombin increased out to day three before declining through the remaining storage time. For room temperature samples, endogenous thrombin potential and peak thrombin declined throughout storage, significant by day three. “So you had greater thrombin generation potential in the cold-stored products,” Dr. Hudgins said.

In cultures performed at 35 days, the authors found no contamination in the refrigerated cryoprecipitate samples. Colonies were detected 48 hours after plating on two of four plates prepared directly from room temperature cryoprecipitate, and no growth was detected in broth cultures prepared from the same samples.

The authors wrote that their study “and others cited demonstrate sufficient evidence to increase the shelf life of cryoprecipitate, but absolute shelf life and proper storage temperature remain up for debate.” They continued, “Our results show that refrigerated cryoprecipitate could safely be extended to at least 14 days, but even at 35 days there is acceptable efficacy in emergency situations or resource-constrained environments.”

Wagner, et al., evaluated whether inoculation of bacteria at levels thought to contaminate whole blood at time of collection can lead to the presence of bacteria capable of proliferation in thawed cryoprecipitate stored at room temperature for an extended period (Wagner SJ, et al. *Transfusion*. 2019;59[11]:3549–3550). Two whole blood units collected from healthy donors were pooled, mixed, and separated into two identical units. One unit was inoculated with one of nine organisms at low levels. Fresh frozen plasma was first prepared from the contaminated and uncontaminated whole blood units, then used to prepare cryoprecipitate, and both units of cryoprecipitate were frozen and later thawed. Cryoprecipitate prepared from the uncontaminated unit of whole blood was inoculated with a similar number of organisms as those inoculated into the whole blood unit. Thawed cryoprecipitate units from the contaminated whole blood and contaminated cryoprecipitate unit were stored for five days at room temperature, and 8-mL samples were used to inoculate two bottles for automated blood culture.

The authors reported that all cryoprecipitate inoculated units were consistently culture positive. They write, “These results strongly suggest that there is a risk of bacterial contamination and proliferation potential in cryoprecipitate stored at room temperature for an extended period. Use of pathogen-reduced cryoprecipitate or bacterial-tested cryoprecipitate may mitigate this risk.”

The Food and Drug Administration in 2020 approved the Intercept Blood System for Cryoprecipitation, used to produce pathogen-reduced cryoprecipitated fibrinogen complex, which has a five-day room temperature expiration.

“The processing for the pathogen-reduced cryoprecipitate is a little different than that for standard cryoprecipitate in that the plasma goes through the pathogen-reduction component; the rest of the cryoprecipitate production remains the same,” Dr. Hudgins said.

The safety and purity concerns are similar to those for pathogen-reduced platelets due to room temperature storage post-thaw, he said. Potency concerns center on the concentrations of fibrinogen, factor VIII, vWF, or factor XIII with prolonged storage. “As we’ve seen with other components, pathogen reduction typically does affect it,” he said, “and we want to make sure we are not reducing these components to a point where we can’t use them.”

The FDA-approved method for cryoprecipitate preparation is amotosalen; the other uses riboflavin, which has not been approved or cleared, Dr. Hudgins said. “The process affects the amount of coagulation factors available in the product,” he said, but “it does not reduce them to a point that would be considered unusable from the standpoint of FDA or AABB standards.” Studies have confirmed that coagulation factors exceed European and U.S. requirements for fibrinogen or factor VIII in cryoprecipitate, he added.

“Pathogen-reduced cryoprecipitate also minimizes dilutional coagulopathy and generates more thrombin than fibrinogen concentrates alone, so it might actually be more beneficial to use this over the fibrinogen concentrate as a whole,” Dr. Hudgins said. “And that in vitro effect is seen continually out to about 10 days, at 20 to 24 degrees.”

As always, sterility is a concern for products held at room temperature. “Pathogen-reduced cryoprecipitate did remain sterile throughout its entire life and beyond,” he said, but the five-day post-thaw shelf life allows for more sustainability for an immediate thaw (Lu T, et al. *Pathogens*. 2022;11[7]:744).

Pathogen reduction use does not eliminate the risk associated with bacterial contamination, Dr. Hudgins noted. “So we cannot reduce our vigilance in looking for potential bacterial contaminations even when we’re looking at our pathogen-reduced products.”

In addition to its higher cost, extended-life cryoprecipitate has other cons: reduced recovery of inherent coagulation factors, though “at this point the functionality of those products does seem to be equivalent to products available already”; increased degradation of labile coagulation factors; contamination that remains possible outside manufacturing; and there is no concurrent culture. Of the latter, Dr. Hudgins said, “Secondary pathways that are available to us in the platelet pathway are not readily available to us in the cryoprecipitate pathway, and it may be something we want to continue to ask about and direct toward the FDA.”

Like cryoprecipitate, liquid plasma allows for a longer period of use of a plasma product that shows hemostatic potential generally equivalent to or better than that of thawed fresh frozen plasma, Dr. Hudgins said.

Liquid plasma has never been frozen, is produced from whole blood or apheresis collections, and can be stored at 1°–6°C with a shelf life of 26 or 40 days. “The FDA says that it’s five days after the expiration of the whole blood unit it’s collected from,” Dr. Hudgins said. Liquid plasma has been available in Europe for a long time, he added, and used in Sweden for urgent cases since the early 1980s.

Gosselin, et al., evaluated liquid plasma's hemostasis and hemostatic potential and found it diminishes after about 14 days (Gosselin RC, et al. *Transfusion*. 2013;53[3]:579–590). Though the FDA approval is for use up to 40 days, limiting overall use to 14 days is recommended. "That's still significantly longer than what you would get from a thawed plasma unit," Dr. Hudgins said.

Liquid plasma storage is associated with some contact activation increase, he said. "That might have some elements to do with it being a cellular product, so you will have platelet micelles and small platelet fragments . . . that may have some increased effect," which is seen in women more than in men.

Gosselin, et al., found that liquid plasma maintains at least 50 percent of factor activity and thrombin-generating capacity up to 15 days of refrigerated storage. "So it would still be a functional element for use in surgical cases," Dr. Hudgins said. "After that you start to see significant decreases in a number of labile factors" (factors V, VII, and VIII, and vWF). Protein S anticoagulant activity also decreases.

"The prominent usage should be up to 15 days."

The AABB, American Red Cross, America's Blood Centers, and Armed Services Blood Program recommend liquid plasma be used solely for massive transfusion in patients with life-threatening hemorrhages. They don't mention trauma, Dr. Hudgins noted, because "we have a lot of different use cases for large-volume transfusions in the hospital, and liquid plasma can be used for smaller hospitals and for more rural locations that may need a protracted time frame for the use of these products."

Matijevic, et al., characterized the changes in liquid plasma hemostatic potential during 26 days of cold storage and reported the hemostatic profiles to be better and sustained five times longer than thawed plasma, indicating that never-frozen plasma can be considered for use in trauma patients requiring immediate plasma resuscitation (Matijevic N, et al. *J Trauma Acute Care Surg*. 2013;74[1]:84–91).

The slight cost increase for liquid plasma can be offset in some hospitals by reduced overall wastage, Dr. Hudgins said. "Each blood bank has to perform its own cost-benefit analysis to assess whether pathogen-reduced cryoprecipitate or liquid plasma is particularly helpful."

Amy Carpenter is CAP TODAY *senior editor*.