e-Network Forum
CALIFORNIA BLOOD BANK SOCIETY
"We help save lives of people who need blood"

Experience in the use of THAWED PLASMA

A transfusion medicine physician in California reports that in November of 2004, his hospital (**located in Los Angeles County**), which is a **Level I Trauma Center**, began to routinely stock "THAWED PLASMA" in order to shorten the turn around time necessary to dispense plasma for emergency transfusions. The THAWED PLASMA inventory (which is also available for routine transfusions) may be prepared from either traditional Fresh Frozen Plasma (FFP) or from 'PLASMA Frozen within 24 Hours after Phlebotomy' (FP24). The THAWED PLASMA can be stored refrigerated for five days, since most clotting factors are stable, although levels of Factor VIII may drop to 60% of pre-storage values (reference). The reduced levels of Factor VIII should NOT present a clinical problem since **residual levels of FVIII in THAWED PLASMA are usually adequate for trauma victims**. Infants who require plasma transfusions and neonates who require exchange transfusion continue to receive plasma that is thawed immediately before the product is needed for transfusion. Consultation with a transfusion medicine physician is encouraged if special handling of plasma is needed for a patient over 4 months old for whom there is a need for the patient to receive plasma containing 100% levels of Factor VIII.

Additional information about THAWED PLASMA can be found in the following links:

- Minimizing wastage of unused thawed FFP
- Relabeling thawed FFP as thawed plasma
- Proper thawing technique when preparing FFP for transfusion
- Expiration date of plasma frozen within 24 hours?
- How best to manage plasma products that are returned unused and how to minimize wastage of plasma products

The California physician wonders **if other institutions are also using THAWED PLASMA**, and if so, what has been the experience?

The following comments have been received.

1. **Dr. John Hess at the University of Maryland** (attribution used with permission) reports that his institution **does not differentiate between FFP and FP24**. In addition, they maintain a large stock of THAWED PLASMA, which they **store for up to 5 days in the refrigerator**, and use whenever plasma is requested, with few **exceptions (e.g. children, liver transplants**). His trauma center uses over 5,000 plasma units/year, but only 5% of acute trauma admissions get plasma (Como et al., Transfusion 2004;44:809-13) which represents a third of their annual plasma usage. Children get plasma that has been thawed less than 24 hours.

2. **A transfusion medicine physician in Boston** would like to emphasize that FFP, as opposed to THAWED PLASMA, may offer benefits for some patients and these **benefits may not be directly related to coagulation factor levels**. Specifically, he is referring to **infants on cardiopulmonary bypass**. He points out a recent study (Mou SS, et al, NEJM, 2004;351:1635-44) that demonstrated that priming the cardiopulmonary bypass pump with fresh whole blood as opposed to reconstituted whole blood containing FFP + RBC resulted in greater positive fluid balance and longer time in the ICU post-op. Unfortunately, the authors of that paper did not report any measurements related to the coagulation cascade. However, there was no significant difference in chest tube outputs and transfusion requirements between the two groups, which suggests that clotting factors were not responsible for the difference between the two groups. While there are other possible explanations for the findings in that study, one possibility is that several factors/proteins are preserved better frozen than in whole blood stored for no more than 48 hours and that some of these factors are clinically relevant in this patient population. For this reason, he thinks it **important that FFP be available** for this selected group of patients and he **agrees with the California physician in Los Angeles County whose institution's policy is to provide FFP as opposed to THAWED PLASMA for neonates**.

3. **A Chief Medical Officer at a community blood center** had first hand experience with a THAWED

PLASMA inventory at a busy hospital in **Atlanta Georgia**. She found that stocking THAWED PLASMA was **incredibly useful to the ER patients and doctors, and it rarely expired unused**, as there were so many patients using plasma that the blood bank was able to rotate the inventory successfully. The medical technologists were happy with the arrangement as it let them prioritize their time elsewhere than thawing plasma continuously. (The institution **presented an abstract at the AABB** after measuring levels of coagulation factors in representative samples of THAWED PLASMA at each day of storage - **data they supplied to the clinicians**, so that they would feel comfortable using the product in adult patients.) The only exception is that **neonates all receive freshly thawed FP24**. She concludes that this process has worked efficiently and well for several years now.

4. **Dr. Ravi Sarode at Parkland Hospital in Dallas, Texas** (attribution used with permission) reports that his institution has been **using THAWED PLASMA for 4 years** after a study from Case Western showed that all clinically important clotting factors including FV are stable at 4C for 5 days except for FVIII. FVIII is an acute phase reactant and patient presenting with trauma or liver disease (acute and chronic) have higher levels. Therefore, thawed plasma can be transfused for correcting coagulopathy in these patients. Plasma is NOT used to treat hemophilia A. Even in newborns FVIII is high. They **keep 4 units of group A and group O and 2 units of group AB plasma always thawed for emergency use and rarely waste any** plasma due to "outdating". He concludes that in his clinical practice, maintaining an inventory of available plasma is fine.

ADDENDA Mar. 22, 2005

5. **A colleague close to the FDA** and familiar with the Code of Federal Regulations reminds us that **THAWED PLASMA is not a licensed blood product**. IT SHOULD NOT BE SHIPPED ACROSS STATE LINES.

ADDENDA Mar. 23, 2005

6. **A transfusion medicine physician in Washington State** is affiliated with a hospital network that relies on a centralized blood bank for essentially all of their plasma products. The central blood bank thaws and then ships 'liquid' FFP to its customer hospitals on demand. The Washington physician reports that their **hospital network's trauma center has been able to reduce wastage of FFP by extending the storage of the product as THAWED PLASMA**; they have been using THAWED PLASMA for the last 6 months. They continue to **use FFP at their other sites where there is only a minimal trauma load**, mostly because the non-trauma sites have minimal wastage of plasma products.

ADDENDA Apr. 3, 2005

7. **A transfusion medicine physician at a very busy Level I Trauma Center in Boston** reports that she is **currently validating** THAWED PLASMA for the same purpose as described by the Los Angeles physician, using data from Downes and colleagues as a basis. The Boston physician's initial validation data show a larger drop in FVII levels in stored THAWED PLASMA than has previously been reported, and she is testing more units to confirm her observation. However, even though in her experience plasma levels of FVII and FVIII both drop as THAWED PLASMA is stored, she is not concerned, since most THAWED PLASMA transfusions would occur in the following clinical situations (Dzik and Rao. Why do physicians request fresh frozen plasma? Transfusion 2004; 44:1393):

   - Before a procedure for a patient with an elevated INR
   - Bleeding and elevated INR
   - Reversal of Coumadin effect before a procedure
   - Factor deficiency (includes liver disease)
   - Coumadin therapy and bleeding
   - Prophylaxis (nonbleed)
   - INR > 3

   However, she does **NOT plan to use THAWED PLASMA for TTP exchanges**, although she is not aware of specific data.

ADDENDA Mar. 1, 2007

8. **The technical manager of a blood transfusion service in Ohio** reports that his hospital will be converting thawed FFP to Thawed Plasma to extend the shelf life of the product. Currently, they employ a trauma protocol for patients with coumadin overdose that includes the administration of plasma within 2 hours of the patient's presentation to the ER. They believe that maintaining an inventory of Thawed Plasma will permit them to provide an adequate turnaround time for patients requiring emergency plasma transfusions. They do not anticipate any problems with maintaining a stock of group A, O, or B Thawed Plasma. However, this might not be the case for group AB plasma. They would like to keep a minimum stock of two group AB Thawed Plasma, but many of their group AB FFP is prepared by apheresis. It is the inquiring **colleague's understanding that the FDA considers FFP prepared by apheresis methods as a product that has a shelf life of 24 hours once it is thawed so these products cannot be converted to Thawed Plasma with a 5**

day shelf life. He wants to know if his belief (that apheresis plasma cannot be stored for 5 days once thawed) is true or false, and **if true, what is the exact citation for this limitation**.

ADDENDA Mar. 6, 2007

9. **Dr. Rob Davenport, Director of Transfusion Medicine Services at the University of Michigan** (attribution used with permission), reports that Thawed FFP or FP24 collected by apheresis **may not be stored beyond 24 hours if collected using an open system**. He obtained the following information (see attached table) from **personal communications with the FDA**. The definitions of open and closed are from the same source. Because the method of collection is not indicated on the product labels, transfusion services should **contact the supplier to determine the method of collection**.

ADDENDA Mar. 7, 2007

10. **A transfusion support manager for a multi-state blood collection agency** reports that a further complicating issue to the use of thawed apheresis plasma is that **many blood suppliers use more than one method/instrument** for collecting and preparing these products yet label the product with the **same product code number**, e.g., 18211. If multiple methods are used by the supplier (or the supplier of the supplier!), the transfusion service would need to obtain this information on a unit by unit basis. Although the blood supplier is able to link a donation to a particular instrument, collection set lot number, etc., this information is not necessarily available electronically and therefore not easily retrievable or available on a unit number by unit number basis, particularly at the distribution point. The respondent **wonders if it will be easier after implementation of ISBT 128** since ISBT 128 assigns a different product code if an opened system is used. This information would then be available on the product label as well as captured electronically and computer tables could be configured to apply the appropriate "rules" for product dating after thawing.

ADDENDA Mar. 17, 2007

11. Written correspondence from **CBER/FDA's Office of Communication, Training and Manufacturers Assistance (OCTMA)** has been provided for this discussion.

> "The information below applies the shelf life of plasma after it has been thawed from the frozen state.
>
> According to FDA regulations, FFP must be given within 6 hours after thawing (see 21 CFR 606.122(m)). There is no change in product name; only the expiration date is changed to 6 hours. Blood centers that want to issue this product within 24 hours after thawing must apply and be approved for an alternative procedure under 21 CFR 640.120. Again there is no change to the product name (it is still labeled as FFP after thawing); only the expiration date is changed to 24 hours. However, we have no objection if the center wants to put the word 'thawed' in front of the FFP product name.
>
> Most centers freeze plasma within 8 hours after collection. Some licensed centers have received approval to freeze plasma collected from whole blood within 24 hours after collection. This product is called Plasma Frozen within 24 hours after Phlebotomy (FP24). FP24 can be used in place of FFP for all indications except replacement of labile coagulation factors (FV and FVIII), so the comments above about the shelf life of FFP after thawing also apply to FP24. [Note that FDA has not approved for plasma collected using automated apheresis instruments to be frozen within 24 hours after collection. This product cannot be distributed in interstate commerce. At this time, the plasma collected using automated apheresis instruments must be frozen within 6-8 hours of collection, depending on the instructions for the storage bags.]
>
> After being thawed and stored at 1 - 6 C for 6 or 24 hours, depending on whether the center has received the 24 hour approval, the plasma can no longer be labeled as FFP or FP24.
>
> We are aware that AABB has designated a product in their Circular of Information and standards called Thawed Plasma that has a 5 day expiration date after thawing. Please be advised that FDA has not received any applications to evaluate the safety and effectiveness of this product, therefore this is not an FDA-approved product. This product cannot be distributed in interstate commerce and the license number on the original label must be removed.
>
> The information above only applies the shelf life of plasma that was collected and prepared in a closed system. Plasma (FFP or FP24) collected or prepared in an open system may only be stored for up to 24 hours (> 6 hours with FDA approval) after thawing."

Please submit comments to the e-Network Forum.

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Posted: March 21, 2005

Addenda: Mar. 21, 22, 23 & Apr. 3, 2005; Mar. 1, 6, 7 & 17, 2007