

# Fresh Frozen Plasma and Variants

D. Joe Chaffin, MD

www.bbguy.org

- I. Topics for discussion:
  - A. Production
  - B. Clinical Uses
  - C. Potential Complications
- II. Production of Fresh Frozen Plasma and Variants
  - A. Definition:
    1. Fresh Frozen Plasma (FFP) is defined in the United States as plasma that is removed from a donor, separated, and frozen within eight hours of collection (or six hours, if ACD is the anticoagulant/preservative)
    2. “Frozen” within eight hours?
      - a) Applicable standards do not require the product to be FROZEN by eight hours, just to be placed at the appropriate temperature
      - b) AABB Standard 5.7.5.9: “Fresh Frozen Plasma shall be prepared from a whole blood or apheresis collection and **placed at**  $\leq -18^{\circ}\text{C}$  within the time frame required for the anticoagulant or collection process” (emphasis mine); *Standards for Blood Banks and Transfusion Services*, 26th ed, 2009.
      - c) FDA 21CFR640.34(b): “...The plasma must be separated from the red blood cells or collected by an apheresis procedure, and **placed in a freezer** within 8 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system, and stored at  $-18^{\circ}\text{C}$  or colder” (emphasis mine).
    3. Why “Fresh”?
      - a) Product is frozen relatively quickly in an attempt to preserve the “labile coagulation factors” (primarily factors V and VIII) as much as possible
      - b) As will be seen later, this is less of an issue than previously thought, and variants of FFP in the US (and all FFP in Europe) with longer pre-freezing intervals are now used
  - B. Contents
    1. Volume:
      - a) Traditional “whole blood derived” FFP: Approximately 200-250 mL
      - b) Apheresis-derived FFP: Varies, can be as high as 700-800 mL if from apheresis single-donor plasma collection
    2. Coagulation factors:
      - a) FFP contains one international unit/ml (IU/ml) of all coagulation factors, except for fibrinogen
      - b) Fibrinogen is measured in *milligrams* rather than IU; FFP contains approximately 400 mg of fibrinogen per unit
    3. Other proteins:
      - a) Also contains anticoagulant proteins and ADAMTS13 (discussed later)
      - b) Though not used for therapeutic benefit, FFP has a relatively full complement of all other plasma proteins, including immunoglobulins and albumin
      - c) These proteins may cause problems with allergic reactions (ranging from mild urticaria to anaphylaxis) in patients who lack particular proteins (IgA is the most famous example)
    4. Unlike many other blood products, there is no quality control (QC) requirement for FFP in the United States
      - a) The above does not mean that we just make it without care; just that in the US, there is no FDA, AABB, or CAP requirement to test a certain number of units every month to make sure that the above contents are reproducibly present

- b) Europe, on the other hand, *does* have QC requirements for FFP
  - (1) All units checked for volume (must be +/- 10% of stated volume)
  - (2) Check Factor VIII levels in ten random units in their first month of storage (>70% levels required)
  - (3) 1% of all units (at least 4/month) checked before freezing for residual RBCs, WBCs, and platelets
- C. Collection methods
  - 1. Whole blood derived
    - a) The traditional manner of FFP preparation
    - b) Each unit of whole blood can result in preparation of a single unit of FFP (in addition to a single unit of red blood cells and a single unit of whole blood-derived platelets)
  - 2. Apheresis derived
    - a) Becoming considerably more common in modern blood banking
    - b) Apheresis: An automated process by which anticoagulated whole blood is removed from the body and separated into individual components, with harvest of a specific component (or components) and return of the remainder of the blood components to the donor
    - c) Plasma can be the primary target of the apheresis procedure, or (more commonly) it can be collected in addition to another target (such as platelets or red blood cells, or both)
      - (1) When not the primary collection target, the collected plasma is technically designated as “concomitant plasma” (also called “concurrent”)
      - (2) All major apheresis equipment manufacturers in the US produce equipment that allows for concomitant plasma collection
        - (a) Fenwal: Amicus and ALYX
        - (b) Caridian (Gambro): Spectra, Trima, and Trima Accel
        - (c) Haemonetics: MCS+8150, MCS+9000
      - (3) Fenwal and Haemonetics also make apheresis equipment for primary collection of multiple units of plasma
- D. Processing
  - 1. Whole blood FFP
    - a) Can be processed manually or via newer, automated whole blood processing equipment
    - b) Plasma separated from red cells via centrifugation, expressed from main bag into a separate bag
      - (1) In the US, when not preparing whole-blood derived platelets, this is done in a refrigerated centrifuge (1-6 C) using a “heavy spin” (5000 x g)
      - (2) Plasma is then expressed into a satellite bag
    - c) Plasma frozen as outlined above
    - d) Note that FDA requires a way to tell if plasma has been inadvertently thawed. This is done by freezing with a rubber band that is then removed, or freezing units on their side and storing them upright
  - 2. Apheresis FFP
    - a) Apheresis equipment separates components (red cells, platelets, plasma) automatically
    - b) No additional centrifugation steps are necessary
    - c) Same thaw-detection methods are used as were outlined above.

- E. Storage
  - 1. Shelf life
    - a) In US, FFP is stored at  $\leq -18^{\circ}\text{C}$  for up to twelve months
      - (1) With approval from FDA, can also store FFP for up to seven years at  $\leq -65^{\circ}\text{C}$
    - b) In Europe, shelf life is more complicated
      - (1) If at  $\leq -25^{\circ}\text{C}$ , can store FFP for up to thirty-six months
      - (2) If at  $-18^{\circ}\text{C}$  to  $-25^{\circ}\text{C}$ , can store for only up to three months
  - 2. Thawing and post-thaw storage
    - a) Thawing is done at  $30-37^{\circ}\text{C}$  in water bath or FDA-approved microwave device
    - b) Storage after thawing is at  $1-6^{\circ}\text{C}$
    - c) FFP shelf life post-thaw is 24 hours
    - d) Beyond 24 hours, product may still be used (see “thawed plasma” below)
- F. Plasma variants
  - 1. Plasma frozen within 24 hours of collection (FP24)
    - a) US blood product that differs from FFP in one main way:
      - (1) FP24 is placed in the freezer in **24 hours** as opposed to **8 hours**
      - (2) This lessens the pressure on blood centers to have units processed rapidly and in the freezer within the 8 hour time period
    - b) Considered equivalent to FFP clinically
      - (1) Does have slightly decreased Factor V (less than 10% decrease) and moderately decreased Factor VIII (20-50% decrease) levels in comparison to FFP
      - (2) Because of the decrease in Factor VIII, FP24 is probably not advisable to use in patients with hemophilia A when no Factor VIII concentrate is available
      - (3) Some also advise not using in patients with DIC
    - c) Storage and shelf-life after thawing identical to FFP (except without the option for storage at  $\leq -65^{\circ}\text{C}$ )
    - d) Interesting to note that in Europe, plasma can still be called FFP even if frozen at 24 hours after collection
      - (1) This is due to the fact that whole blood derived platelets in Europe are most commonly made using the “buffy coat method,” which requires that units of whole blood sit overnight at room temperature before platelets are made
  - 2. Plasma
    - a) Plasma removed from liquid whole blood between 24 hours after collection and up to five days after the expiration of the whole blood unit
    - b) Product is stored frozen (see “Liquid Plasma” below) at  $\leq -18^{\circ}\text{C}$  for up to 5 years
      - (1) Note that FFP not used within 1 year can be re-labeled as “plasma” and kept up to 5 years from original collection date
    - c) Rarely used for transfusion; often re-labeled as “recovered plasma”; see below
  - 3. Liquid Plasma
    - a) Plasma removed from liquid whole blood up to five days after the expiration of the whole blood
    - b) Product is stored refrigerated and expires at day 5 after the parent whole blood unit expires
    - c) Rarely used for transfusion
  - 4. Cryo-reduced plasma (CRP)
    - a) In order to produce Cryoprecipitate (CRYO, Antihemophilic Factor/AHF), FFP is thawed at  $1-6^{\circ}\text{C}$ , and a small amount of solid material (precipitate) is left behind.
    - b) The fluid that is *removed* (all but about 15 mL) is called “cryo-reduced plasma”
      - (1) Also known as “cryo-poor plasma” and “cryosupernatant.”

- c) CRP contains decreased levels of the components of CRYO (fibrinogen, factors VIII and XIII, and von Willebrand's factor) but near normal levels of the rest of the coagulation factors
  - d) CRP really has only one main use: For transfusion or fluid replacement in cases of thrombotic thrombocytopenic purpura (TTP; see below)
  - e) Storage times are identical to those for FFP
5. Thawed plasma
- a) After 24 hours, according to AABB, may re-label a whole-blood derived FFP or FP24 product as "thawed plasma" and keep at the same storage conditions for up to five days from the time of thawing
  - b) Considered by most to be functionally equivalent to thawed FFP, and is used interchangeably in most clinical situations
    - (1) Moderate decreases in both Factor V and Factor VIII are seen
    - (2) Roughly half the levels present at the time of thawing are seen at the 5 day expiration time
    - (3) However, this is not seen as an impediment to the use of the product, as factors remain in the range that can still induce hemostasis
  - c) Potential cautions
    - (1) Same cautions as above; probably not great for factor VIII replacement and possibly not useful in patients with DIC
  - d) How does the FDA feel about thawed plasma?
    - (1) FDA does not recognize thawed plasma and takes no position on it either way
    - (2) AABB has taken a stand and says it is acceptable to re-label thawed FFP and keep 1-5 days
    - (3) While this seems contradictory, this functionally means that blood banks can't *license* the product with FDA, but can use it in their own transfusion services
6. Source plasma
- a) Product collected by apheresis, generally from paid donors
  - b) Intended for manufacture into either injectable or noninjectable products; definition excludes products designed for direct transfusion
  - c) Donors are screened for same infectious diseases as regular blood donors except HTLV
  - d) Licensed product collected only by licensed facilities
7. Recovered plasma
- a) Plasma separated from volunteer whole blood donation (in contrast to source plasma discussed above)
  - b) Unlicensed product
  - c) Unused units of FFP, FP24, or plasma may be re-labeled as recovered plasma at any time
  - d) Blood centers may use recovered plasma as source of revenue, selling product for further manufacture through "short supply agreements" with plasma companies
8. Donor-retested plasma
- a) Another uncommonly used plasma product
  - b) The idea is that the donor must be screened twice for infectious disease before his plasma is released for transfusion
  - c) Unit of plasma is *held* until the donor has been re-tested at a regular donation interval (at least 56 days); if negative, first unit is released
  - d) Cool idea; not used very often

9. Solvent/detergent-treated plasma (SDP)
    - a) Pooled plasma product treated to remove viruses; no longer available in the United States
    - b) Manufactured product made from plasma from up to 2500 donors pooled together
    - c) Product is then treated with a solvent and a detergent to remove enveloped viruses
      - (1) This includes HIV, Hepatitis C, Hepatitis B, HTLV
      - (2) Does not include Hepatitis A or parvovirus B19
    - d) Significantly decreased levels of certain coagulation factors, including protein S
- III. Clinical uses of FFP and variants
- A. General principles
    1. Two main reasons to use FFP
      - a) Therapeutic
        - (1) Several fairly well-accepted indications will be outlined below
        - (2) This category includes situations where a patient is bleeding and has significant coagulation factor deficiencies
        - (3) Also includes specific situations where FFP is used to replace patient plasma in apheresis (such as thrombotic thrombocytopenic purpura)
      - b) Prophylactic
        - (1) This category includes transfusions that are done to prevent bleeding in patients with coagulation factor deficiencies
        - (2) Transfusions of this type have been increasing in frequency for a number of years now, and they represent the area where the most possible improvement in plasma transfusion practices can be made (see below)
    2. Dosage
      - a) At some point, providers became convinced that 2 units of FFP was an appropriate dose for pretty much any coagulopathy (probably because it's easy to remember!)
      - b) In most cases, this is serious under-dosage!
      - c) Effective dose: 10-20 ml/Kg body weight
        - (1) 70 Kg patient: 700-1400 ml of FFP recommended when FFP indicated (see below)
        - (2) This represents somewhere between 3 and 7 units of typical-volume FFP in a person who weighs about 150 pounds!
    3. Pretransfusion testing
      - a) FFP should be ABO-compatible with recipient RBC
      - b) FFP is given without regard to Rh status of donor or recipient
      - c) FFP transfusion does not require a crossmatch (not enough RBCs)
  - B. Well-accepted uses
    1. Bleeding patients with multiple coagulation factor deficiencies
      - a) This is referring primarily to acquired deficiencies rather than inherited ones
      - b) Many possible ways for these to occur, most prominently including massive transfusion (as a result of dilution of coagulation factors), Disseminated Intravascular Coagulation (as a result of consumption of coagulation factors), and hepatic failure (as a result of lack of production of coagulation factors; see discussion below)
      - c) In this setting, FFP is used to replenish the depleted factors

2. Bleeding patients with hepatic failure
  - a) The liver makes most of the important coagulation factors, and hepatic failure/severe liver disease are at risk for severe bleeding as a result
  - b) This bleeding can be generalized or localized, and it can occur without a procedure or with a procedure
  - c) Unfortunately, in these patients, even markedly elevated basic coagulation tests (PT/INR and aPTT) do not predict whether or not a particular patient will bleed
    - (1) People with hepatic failure do not bleed as much as you might expect, given their lack of factor production and elevated coagulation studies
    - (2) This may be due to the fact that their *anti*-coagulant levels decline, as well, from decreased hepatic production
    - (3) So, while they certainly have less substrate force that would *stimulate* them to clot, they also have less substrate force *preventing* them from clotting; a bleeding-free steady state often results
  - d) As a result, FFP transfusion for these patients should be limited to those who are *actively bleeding* and should not be given prophylactically
  - e) In patients who *are* bleeding, doses of FFP given will need to be on the high side (roughly 20 mL/Kg, which translates to at least 6 to 8 units most often)
    - (1) CAUTIONS:
      - (a) Such doses will usually NOT “correct” the abnormal coagulation tests
      - (b) The doses will need to be repeated quite often (every four hours or so), because the liver is not replenishing supplies of the coagulation factors (especially factor VII, which has a very short *in-vivo* half life, roughly 4-5 hours)
3. Warfarin reversal
  - a) Warfarin is an oral anticoagulant used for prevention of recurring thrombosis
  - b) Works by blocking a hepatic carboxylation step for the vitamin K-dependent coagulation factors II, VII, IX, and X primarily
  - c) Effect is reversed by administration of vitamin K
    - (1) Oral, subcutaneous, and intravenous forms if vitamin K available
    - (2) IV form is fastest (several hours), but some are reluctant to use due to reports of anaphylaxis
  - d) Monitored most commonly by the *International Normalized Ratio* (INR), which is calculated from the prothrombin time (PT) and standardized across laboratories
  - e) Two main *possible* scenarios for use of FFP in patients taking warfarin:
    - (1) Non-bleeding patients with elevated INR
      - (a) This scenario does NOT usually require FFP transfusion!
      - (b) Protocol outlined in detail in an article from 2008 (*Chest* 133:160S-198S)
        - i) Non-bleeding patients with INR up to 9.0:
          - (1) Hold warfarin dose
          - (2) Give oral vitamin K if INR  $\geq 5$
          - (3) FFP not indicated!
        - ii) Non-bleeding patients with INR  $\geq 9.0$ :
          - (1) Hold warfarin dose
          - (2) Give higher dose of oral vitamin K
          - (3) FFP not indicated!
        - iii) Bleeding patients at any INR (see below)
      - (c) Mainstays of therapy for non-bleeding patients: Hold warfarin dose and administer vitamin K without transfusing FFP!

- (2) Bleeding patients, regardless of INR
  - (a) Use in this scenario is pretty well accepted, but FFP may not be the best product to use
  - (b) Alternatives: Prothrombin complex concentrate (PCC), recombinant activated factor VII (NovoSeven).
  - (c) Vitamin K should be administered regardless of use of FFP
  - (d) Dose: 10-20 ml/Kg is generally accepted (again, please note that this is MORE than the “typical” two units that are often given in this situation)
4. Thrombotic Thrombocytopenic Purpura (TTP)
  - a) TTP is caused by deficiency of an enzyme called ADAMTS13, a component of normal plasma that normally cuts von Willebrand factor into smaller fragments (a factor-cleaving enzyme)
    - (1) May be acquired (autoantibody vs ADAMTS13) or congenital (production)
  - b) Decreases in this enzyme result in an increase in the presence of “*unusually large von Willebrand Factor multimers!*” (OK, some call them “ultralarge”; I like it either way!)
  - c) These multimers are powerful procoagulants, and their presence results in formation of microthrombi throughout the body, with associated hemolysis of red blood cells
  - d) The diagnostic “pentad” of TTP
    - (1) Fever
    - (2) Thrombocytopenia
    - (3) Renal failure
    - (4) Microangiopathic hemolytic anemia (MAHA)
    - (5) Mental status changes
  - e) Currently, therapeutic plasma exchange (TPE) is the mainstay of TTP treatment (though some patients can get away with just plasma transfusion)
    - (1) Typically done via apheresis equipment, with FFP used as replacement fluid
    - (2) Basic idea: Out with the “bad”, ADAMTS13-deficient patient plasma, in with the “good”, ADAMTS13-rich donor plasma
    - (3) TPE also can remove autoantibodies from circulation in acquired TTP
    - (4) TPE procedures usually continued until platelet count has returned to at least 100,000 (some use 150,000), and lab indicators of hemolysis have normalized (LDH used most frequently)
    - (5) Success rates: Over 90% achieve remission within 3 weeks
    - (6) Some have used “cryo-reduced” plasma (CRP) due to lower levels of vWF in general; this is usually reserved for those who have failed TPE with FFP
5. Replacement fluid in other diseases treated by plasmapheresis
  - a) Uncommonly needed; most patients tolerate plasmapheresis without the need for FFP replacement to replenish coagulation factors
  - b) Seen with intense, repeated plasmapheresis
6. Specific factor deficiencies without an available factor concentrate
  - a) These are becoming fewer in recent years as more and more factor concentrates have become available
  - b) The short list of deficits that can’t be treated with a purified concentrate include:
    - (1) Factor V deficiency
    - (2) Factor X deficiency
    - (3) Factor XI deficiency
    - (4) C1 esterase inhibitor deficiency (hereditary angioedema)

- c) Smaller facilities that do not stock some of the available purified factor concentrates may be forced to give FFP in emergency situations until the purified product can be acquired
- C. Controversial/nonstandard uses for FFP
1. Prophylactic treatment for the mildly elevated PT/INR ( $\text{INR} \leq 2.0$ )
    - a) I have deliberately placed this discussion below that of warfarin reversal
    - b) Note in the above discussion that even very high INR values do not usually result in a need for transfusion of FFP/PCC
    - c) Let's be consistent: You can't say that a patient with an INR of 1.5 is not sufficiently anticoagulated when you are treating him for thrombosis prevention, then turn around and say that another patient with an INR of 1.5 needs an FFP transfusion because he *is* anticoagulated!
    - d) Plasma transfusions for mildly elevated PT/INR levels ( $\text{INR} \leq 2.0$ ) both prophylactically and prior to bedside/interventional procedures have been studied retrospectively and are being studied prospectively. Here are the main issues raised:
      - (1) No evidence of correction of lab values
        - (a) Most people under-dose in this situation
        - (b) The closer an INR is to normal, the more plasma is needed to "correct" the value
        - (c) Traditional 2 units of FFP order is clearly not enough!
        - (d) As a result, retrospective (and recent prospective) studies have shown "correction" of PT/INR in less than 5% of patients transfused for this reason
      - (2) No evidence of prevention of bleeding
        - (a) OK, so even if the lab values are not "corrected," some might argue that FFP "will keep a patient from bleeding, right?"
        - (b) Same studies showed NO DIFFERENCE in bleeding rates for patients who were given FFP in comparison to those not given FFP
          - i) To be fair, these studies are hampered by the fact that they are virtually all underpowered (not as many patients as we would like), and are virtually all retrospective
          - ii) Higher-powered, prospective, randomized studies are planned and ongoing now
      - (3) CONCLUSION: Based on currently available data, prophylactic FFP transfusion is NOT indicated for correction of mildly elevated PT/INR lab values, even if bedside procedures are contemplated
  2. Prophylactic treatment for mildly elevated PT/INR prior to surgery
    - a) Much of the data referenced in the item above for purely prophylactic FFP applies for mildly elevated PT/INR values prior to surgical procedures
    - b) The main problem, again, is that mild PT/INR elevations are NOT good predictors of whether a patient will bleed during surgery
    - c) As a result, there is no evidence that transfusion of FFP in this situation improves outcomes or lessens bleeding
    - d) Standard guidelines from American Society of Anesthesia recommend no consideration of correction for  $\text{INR} \leq 2.0$
  3. Voodoo and silly stuff
    - a) Volume replacement
      - (1) There are obviously effective ways to increase a patient's blood volume without exposure to someone else's plasma

- (2) This is unfortunately one of the most common misuses of FFP
  - b) Wound healing
    - (1) No evidence that FFP aids wound healing
  - c) “My patient just feels better”
    - (1) I don’t know how to even *start* to address this one...
  - d) Nutrition
    - (1) FFP is not an acceptable way to correct a low protein level or hypoalbuminemia or immunodeficiency, etc., etc., etc.
- D. Trauma and massive transfusion
1. Current “hot topic”
    - a) This is a huge issue, with the potential to transform trauma-related transfusion medicine completely
    - b) Huge amounts of research being done to define the best process
  2. Historical trauma transfusion management
    - a) Many blood banks dealt with transfusion in trauma in a “reactive” manner; doling out blood products when indicated by laboratory tests or when clinical bleeding necessitated a “shotgun” approach
      - (1) Several problems with this approach:
        - (a) Timeliness of monitoring
          - i) By the time lab values are back, the patient’s situation may have changed dramatically
          - ii) This is especially true in situations where point-of-care lab testing is not available
          - iii) Making transfusion decisions based non-current data is inefficient and potentially dangerous
        - (b) Lack of consistency
          - i) Plasma products often were ordered when someone happened to think about it, leading to patients who were under-transfused FFP in relation to RBCs
          - ii) The “shotgun” approach, quite frankly, is a miserable way to transfuse!
  3. The “proactive approach”: The military takes the lead
    - a) Initial study published in 2006 (*J Trauma* 2006;60[suppl]:S91-S96) suggested that a standardized protocol was needed for trauma, and suggested that a red cell to FFP to platelet concentrate ratio of 1:1:1 was optimal
      - (1) The idea was to *avoid* trouble rather than *respond to* trouble
      - (2) This strategy has been called “damage control resuscitation”
    - b) Combat study published in 2007 (*J Trauma* 2007;63:805-813) showed that the closer a combat trauma patient was to a 1:1 ratio of red cells to plasma transfused, the better their survival
    - c) This unleashed a storm of studies in the transfusion and trauma literature trying to either prove or disprove this idea
      - (1) These studies, summarized in *Transf Med Rev* 2009; 23:247-254 and 255-265, do not show a clear answer to the question, but there are definitely examples that suggest a survivor benefit from the 1:1 ratio
  4. A few arguments in favor of formula-driven massive transfusion policies:
    - a) Trauma patients have distinctly worse outcomes when they develop the so-called “lethal triad” of **coagulopathy, acidosis, and hypothermia**

- (1) These patients often *present* with an acute coagulopathy related to trauma (estimated 25% of cases), so the 1:1 idea, in part, is designed to combat the first leg of the lethal triad that may already be in place
  - (2) Even if a trauma victim is not *yet* coagulopathic, aggressive FFP transfusion has potential to prevent such coagulopathy
  - b) These protocols keep things simple, lessening the need for urgent communication with an often overwhelmed clinical team
  - c) Patients generally get products more rapidly under formula-driven protocols (especially in places that keep thawed plasma available)
  - d) FFP is more efficient for volume replacement than saline (see below)
  - e) Some studies suggest LOWER total product use overall with these protocols
  5. A few arguments against formula-driven massive transfusion protocols:
    - a) Runs counter to usual transfusion medicine thought of “give the patient only what they need”
    - b) Increased donor exposure is a possibility (though some argue 1:1 protocols result in fewer transfusions overall, as noted above)
    - c) Increased use of AB plasma
      - (1) The plasma that is kept thawed and available is most often AB, obviously because it can be given to anyone
      - (2) AB donors are rare (4% or so of population), so most blood banks are not able to use only plasma from female donors
      - (3) Transfusion-related acute lung injury (TRALI) is more common when recipients get plasma from female donors
    - d) Wastage of plasma from thawed and not-used units
    - e) Original recommendation was 1:1:1 (red cells:plasma:platelets); how does this translate to an era when apheresis platelets are the vast majority?
      - (1) Some have addressed this by giving a unit of apheresis platelets as a standard dose every 6-8 units of RBC/FFP
      - (2) Clinicians can confuse the terminology and expect a unit of platelets per unit of FFP; opportunity for education about apheresis vs. whole blood platelets
    - f) MOST IMPORTANTLY: These protocols have not yet been proven in randomized, prospective studies
  6. Current reality
    - a) Formula-driven protocols are gaining in popularity, and they are probably here to stay for the short-term at least
    - b) Prospective studies are needed to answer the question definitively
    - c) Until then, it's very difficult for blood bankers to argue with the available data
- IV. Potential complications from FFP transfusion
- A. Transfusion reactions
    1. TRALI
      - a) Mentioned above
      - b) Current thought: Most cases caused by two successive events:
        - (1) Sensitizing event that makes the pulmonary circulation ripe for damage, probably by activating neutrophils (massive trauma/transfusion, sepsis, major surgery)
        - (2) Transfusion of blood containing “biological response modifiers” (BRM) that activate the sensitized cells
          - (a) Anti-HLA or anti-neutrophil antibodies
          - (b) Increased amounts of blood breakdown products, including lipids

- c) Resultant pulmonary edema leads to acute respiratory distress/hypoxemia within 6 hours of transfusion
    - (1) Fever, hypotension, and acute (transient) neutropenia are often also seen
    - (2) Symptoms overlap with other entities, including circulatory overload, ARDS, myocardial infarction, pulmonary embolism, etc
  - d) TRALI has been the most common transfusion-related fatality reported to FDA for FY05 through FY08, and FFP the most common associated component
  - e) Multiparous female donors are more likely to have the antibodies mentioned above, so most non-AB FFP transfused in the US today is from either male donors or female donors tested and shown to be negative for anti-HLA/neutrophil antibodies
2. Transfusion-associated Circulatory Overload (TACO)
- a) Acute congestive heart failure secondary to transfusion
    - (1) At-risk patients include very young and very old, patients who already have CHF or other heart disease, patients with volume-compensated chronic anemias
  - b) FFP is particularly likely to cause TACO in susceptible patients due to retention of product in intravascular space
  - c) Easily confused with TRALI
    - (1) TACO usually afebrile; TRALI usually febrile
    - (2) Lack of antibodies or other BRM
    - (3) B-natriuretic peptide (BNP) may help in the distinction
      - (a) BNP elevated in TACO, normal in TRALI
      - (b) Comparison with pre-transfusion levels is most helpful
  - d) May prevent by use of smaller volumes, split units, slower transfusion rates
3. Allergic
- a) Mild allergic reactions are common
    - (1) Type I hypersensitivity to plasma proteins
    - (2) No significant consequence
  - b) Anaphylactic reactions are uncommon
    - (1) Most often seen in IgA-deficient recipients given products that are *not* IgA-deficient
    - (2) For plasma transfusions, these patients require FFP made from IgA-deficient donors
4. Acute Hemolytic
- a) Always a risk in any transfusion, but rare in FFP
  - b) Most are secondary to administration errors (blood product given to wrong patient)
5. Transfusion-associated graft-vs-host disease (TA-GVHD)
- a) Not generally thought to be a risk
    - (1) Traditional belief: No viable white blood cells in FFP
    - (2) Newer data: Uh-oh, there *may* be viable WBCs in FFP
  - b) Despite this, few are irradiating FFP to prevent TA-GVHD
- B. Post transfusion infection
- 1. Plasma-based viruses are most likely to be transmitted via FFP
    - a) The list includes most of the major viruses such as HIV, HBV, and HCV
  - 2. Cell-based viruses are much less likely to be transmitted
    - a) CMV and HTLV have not been reported to be transmitted via plasma

- b) Studies mentioned above showing viable WBCs in FFP suggest at least a possibility of such transmission, however
- 3. Alloimmunization
  - a) Like TA-GVHD and cell-based virus transmission, formation of anti-HLA antibodies in response to FFP transfusion has always been thought to be nearly impossible
  - b) Newer studies have led some to advocate use of leukocyte reduction for FFP in patients at risk for alloimmunization (especially multiply transfused cancer patients)
- V. Summary
  - A. FFP transfusion plays a vital role in treatment of several specific clinical situations
  - B. FFP, however, is easily and commonly misused, especially in situations of mildly elevated coagulation factor tests and prophylactic transfusions
  - C. FFP transfusion in trauma is undergoing major upheaval, with “formula-driven” protocols gaining widespread popularity among clinicians, with transfusion medicine specialists cautiously allowing such protocols
  - D. FFP transfusion is not without complications, with TRALI and TACO being among the more common possibilities

#### SOURCES AND RECOMMENDED READING:

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  - Chapter 20: “Hemotherapy Decisions and Their Outcomes,” pp. 589-593
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  - Chapter 12: “Blood Manufacturing: Component Preparation, Storage, and Transportation,” pp. 196-197
  - Chapter 19: “Fresh Frozen Plasma and Related Products,” pp. 259-269
  - Chapter 35: “Transfusion of the Patient with Acquired Coagulation Defects,” pp. 482-495
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