Best use of plasma components, Part 1: Fresh frozen plasma

Indications, therapeutic guidelines, side effects, and risks

LESLIE C. HUFF, M.D. and THOMAS S. KICKLER, M.D.

ABSTRACT: Transfusion of fresh frozen plasma (FFP) is indicated in a variety of settings, including emergency reversal of warfarin effect and correction of massive bleeding in patients with disseminated intravascular coagulation. Volume replacement is the most common nonindicated use of FFP. During massive transfusion, anticipate requirements of 6 to 8 units of platelets and 3 to 4 units of FFP per every 15 units of red cells administered. In patients with liver disease, FFP administration is appropriate only when there is active bleeding or when surgery is anticipated. When a specific component is unavailable or inappropriate, FFP can be used to manage deficiencies of antithrombin III or factors II, V, VII, IX, X, and XI. Plasma exchange transfusion or infusion of large amounts of FFP is the therapy of choice for patients with thrombotic thrombocytopenic purpura. (J Crit Illness 1989;4(5):37-44)

The role of plasma component therapy is currently in a state of change. There are two major causes of this change. The first is the increasingly conservative and discriminating approach to the transfusion of blood and blood products (Table 1). This approach is the result of increased physician awareness of potential risks and greater knowledge of the limited indications for plasma and plasma derivatives.

The second cause of change is the development of commercially purified plasma fractions. Technologic advances have made large-scale purification and production of these plasma fractions possible. The fact that these plasma products can now be rendered less infectious—or even noninfectious—by various processes has been a major incentive in their development.

This is the first of two articles in which we will discuss the current role of plasma component therapy in critically ill patients. Here we will review the appropriate and inappropriate indications for fresh frozen plasma (FFP) and will offer guidelines for its use in specific clinical situations.

In a coming issue of The Journal of Critical Illness, we will focus on plasma derivatives: cryoprecipitate, intravenous immune globulin, and albumin solutions. We will also describe two new components—fibronectin and antithrombin III—that are currently under investigation.

FRESH FROZEN PLASMA

FFP is defined as the fluid portion of 1 unit of human blood that is separated from the red cells by centrifugation and that is frozen at −18 °C (0 °F) or less within six hours of collection. Units of FFP may be stored at this temperature (the optimal storage temperature is −30 °C [−22 °F] or less) for 12 months, after which the labile clotting factors (V and VIII) may decrease to suboptimal levels. FFP must be agitated while it is thawed in a 30 °C (86 °F) to 37 °C (99 °F) water bath. Thawing takes

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approximately 45 minutes; consequently, there may be critical time delays—especially during emergency surgery.

Methods of rapid thawing using a microwave oven or a 56 °C (133 °F) water bath have been described with thawing times of ten minutes and 28 minutes, respectively, and without loss of function of coagulation factors. Units of FFP that have been thawed in a microwave oven have been administered to patients without adverse effects.

FFP contains all of the labile and stable components of the coagulation system. Units of FFP have an average volume of 200 mL. One unit contains approximately 400 mg of fibrinogen and 175 to 200 units of each of the clotting factors. Thus 1 mL of FFP contains 1 unit of clotting activity. Ideally, 1 unit of FFP should yield a factor rise of 8% and a fibrinogen level increment of 13 mg/dL in a patient with a blood volume of 5 L and plasma volume of 3 L.

The risks of FFP administration include disease transmission, allergic responses that can vary from urticarial to potentially fatal anaphylactic reactions, noncardiogenic pulmonary edema, alloimmunization, and hypervolemia leading to cardiac failure.

**APPROPRIATE AND INAPPROPRIATE USES**

During the 1970s and early 1980s, use of FFP increased dramatically. In response to this increase, the National Institutes of Health (NIH) held a Consensus Development Conference in 1984 to discuss indications for, and risks of, FFP administration. It was suggested that the vast majority of plasma transfusions (perhaps 90%) were inappropriate; the most common nonindicated use was volume replacement when crystalloids or colloids would have been safer and equally effective.

The recommended clinical indications for FFP, as outlined by the NIH consensus panel, are listed in Table 2. Inappropriate uses are also listed in that Table. These recommendations are helpful as a general outline; unfortunately, there is no consensus about specific guidelines for the administration of FFP.

There is much debate about interpreting abnormal parameters of coagulation (and thus determining when FFP is needed) and about appropriate dosing of FFP.

We will therefore attempt to define the clinical indications for FFP and will suggest some guidelines for dosing based on our personal experience.

**Massive transfusion**

The replacement of at least 1 total blood volume (approximately 10 units of blood) within a 24-hour period is considered a massive transfusion. Massive transfusion is most often needed during trauma, surgery, cardiopulmonary bypass procedures, or therapeutic exchange transfusion. It may also be required should bleeding develop in patients with disseminated intravascular coagulation (DIC).

The rationale for FFP administration during massive transfusion is to correct dilutional coagulopathy resulting from the infusion of packed red cells, crystalloids, and/or colloids. In addition to dilution, increased consumption of clotting factors often coexists in patients who have undergone trauma or surgery or who have DIC, for example.

It has also been suggested that the shock insult, as reflected by

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**Table 1 – Plasma products for transfusion**

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<thead>
<tr>
<th>Available</th>
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<tbody>
<tr>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
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<tr>
<td>Intravenous immune globulin</td>
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<tr>
<td>Albumin solutions</td>
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<td>Coagulation factors</td>
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<td>Plasma protein fraction</td>
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<tr>
<td>Investigational</td>
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<td>Fibronectin</td>
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<td>Antithrombin III</td>
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**Table 2 – A guide to fresh frozen plasma component therapy**

<table>
<thead>
<tr>
<th>Appropriate indications</th>
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<tr>
<td>Massive transfusion with hemorrhage and documented coagulation defects</td>
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<tr>
<td>Liver disease with active bleeding and multiple coagulation defects</td>
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<tr>
<td>Replacement of isolated factor deficiencies for which specific component therapy is not available</td>
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<tr>
<td>Emergency reversal of warfarin effect</td>
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<td>Decompensated disseminated intravascular coagulation with bleeding</td>
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<td>Antithrombin III deficiency</td>
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<td>Thrombotic thrombocytopenic purpura</td>
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<table>
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<tr>
<th>Inappropriate indications</th>
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<tr>
<td>Plasma volume expansion</td>
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<tr>
<td>Resuspension medium for packed red cells</td>
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<td>Nutritional source</td>
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<tr>
<td>Prophylactic administration in multiply transfused patients with no documented coagulation abnormalities</td>
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<tr>
<td>Correction of abnormal coagulation in the otherwise stable patient</td>
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</table>
Table 3 – Guidelines for administering fresh frozen plasma in adults during massive transfusion

- Frequently determine platelet counts and obtain coagulation study results.
- Give fresh frozen plasma (FFP) when there is significant laboratory evidence of coagulopathy (such as a prothrombin time and partial thromboplastin time of more than 1.5 times control and hypofibrinogenemia [levels less than 100 mg/dL]) in a patient who has clinical evidence of pathologic hemorrhage (usually generalized microvascular bleeding or oozing) with adequate platelet counts (80,000 to 100,000/μL). Functional platelet abnormalities develop in patients undergoing cardiopulmonary bypass; therefore, these patients may require platelet transfusions.
- Patients receiving whole blood or modified whole blood are much less likely to require FFP than those receiving packed red cells. However, platelet requirements are the same.
- It is reasonable to anticipate dilutional thrombocytopenia and dilutional coagulopathy after administration of about 15 units of red cells in healthy patients who do not have a consumptive process. However, in patients with increased consumption (as a result of disseminated intravascular coagulation or trauma, for example) or in patients with preexisting clotting factor deficiencies (such as in liver disease) or thrombocytopenia, dilutional effects may occur at lower transfusion volumes (such as 5 to 10 units of red blood cells).
- If thrombocytopenia exists, platelets are usually given as 6 to 8 pooled units. These platelet transfusions have a pooled plasma volume of 300 to 400 mL. The plasma contains all of the stable clotting factors and significant amounts of factors V and VIII, roughly equivalent to 1 to 2 units of FFP.
- It has been shown that large volumes (600 to 2,000 mL or 12 to 20 mL/kg) of FFP administered rapidly (over several hours) are required to significantly affect coagulation status in patients suffering trauma or massive hemorrhage. Therefore, if dilutional coagulopathy with hemorrhage exists, an adequate amount of FFP should be requested.
- Following cardiopulmonary bypass surgery, the most common causes of bleeding are thrombocytopenia and functional platelet abnormalities related to the bypass pump, incomplete reversal of heparinization with protamine, or surgery itself. Platelet transfusion is commonly needed post bypass, whereas routine administration of FFP is not.

In most hospitals, however, neither whole blood nor modified whole blood is available in sufficient quantities to supply a patient requiring emergency massive transfusion. As a result, packed red blood cells are administered.

Altered hemostasis that occurs in massive transfusion is caused by dilutional thrombocytopenia more often than dilutional coagulopathy. Significant thrombocytopenia is not usually seen until 15 to 20 units of blood (1.5 to 2.0 times the blood volume) has been given. However, mild to moderate drops in platelet counts can be seen after transfusion of 5 to 9 units. Platelet consumption in some settings (trauma or DIC) may cause thrombocytopenia to occur sooner than expected by dilution alone.

The importance of dilutional coagulopathy associated with massive transfusion is much less clear. Studies have shown that coagulation factor dilution corresponds inconsistently with the amount of transfused red cells. Part of the problem in attempts to correlate numbers of red cell units transfused with abnormal coagulation studies is failure to consider the coexistence of other factors, such as DIC or liver disease.

In a study of 172 cases of massive transfusion, there was no significant difference in coagulation test results in groups of patients receiving 5 to 9 units, 10 to 14 units, and more than 15 units of packed red blood cells and/or whole blood. However, when a subgroup of patients without hemostatic disorders (caused by DIC, liver disease, or heparin, for example) was analyzed, there was a significant correlation between number of units transfused and
depression of platelets and plasma fibrinogen levels, and a prolonged prothrombin time (PT).

In the same study, the authors found that administration of platelet concentrates and/or FFP according to established schedules (such as 1 unit of FFP per every 3 units of whole blood/packed red blood cells, or 3 units of platelets and 2 units of FFP per every 10 units of whole blood/packed red blood cells) was of no value in preventing or reducing the number of coagulation abnormalities. More important, there was no significant difference in whole blood/packed red blood cell requirements between the patients given platelet concentrates and/or FFP on an established schedule and those given only whole blood and/or packed red cells. Administration of blood components based on established schedules thus appears to be unjustified.

Guidelines for FFP administration in massive transfusion are cited in Table 3. Although these guidelines are reasonable, they are almost impossible to follow rigorously because of time delays in awaiting laboratory results and components from the blood bank. For example, if one waits to fill all the criteria in the second guideline before ordering FFP, oozing may continue; by the time FFP is available, there may be further dilution. Therefore, anticipate requirements of 6 to 8 units of platelets and 3 to 4 units of FFP per every 15 units of red cells that are given.

Liver disease
In patients with severe liver disease, multiple hemostatic defects may develop from decreased synthesis of clotting factors—particularly factors II (prothrombin), V, VII, IX, XIII and, in some cases, I (fibrinogen). This problem may be compounded in the alcoholic or malnourished patient by vitamin K deficiency, which leads to decreased production of the vitamin K-dependent factors II, VII, IX, and X. Patients suffering from alcoholism and/or malnutrition may therefore benefit from vitamin K therapy.

Other factors that may contribute to poor hemostasis in patients with hepatic disease include chronic low-grade consumptive coagulopathy, thrombocytopenia caused by hypersplenism/splenic sequestration, and functional platelet abnormalities. The most common laboratory coagulation abnormality in patients with liver disease is a prolonged PT, although other abnormalities are usually present as well.

There is no role for FFP in chronic prophylactic replacement of coagulation factors in patients with liver disease who have only abnormal laboratory findings. FFP is appropriate in patients who are actively bleeding or when surgery is anticipated.

There is no consensus as to what constitutes a safe PT during liver biopsy or elective surgery. As long as bleeding time is normal and/or the platelet count is above 80,000/μL, no replacement therapy (FFP) is likely to be needed if the PT is 1.5 times control or below. Significant correction of laboratory abnormalities may require large amounts of FFP (600 to 2,000 mL or 12 to 20 mL/kg) administered over several hours. An approach to the management of severe bleeding in patients with cirrhosis is given in Table 4.

Isolated factor deficiencies
The NIH consensus panel advocates use of FFP in the management of deficiencies of factors II, V, VII, IX, X, and XI when specific component therapy is neither available nor appropriate. However, it is difficult to achieve hemostatic levels of factor IX with FFP in severely deficient patients.

The therapy of choice for hemophilia B (factor IX deficiency) is factor IX complex, which also contains factors II, VII, and X and can be used in patients with deficiencies of the latter factors as well. However, in factor X deficiency, factor levels of only around 10% are needed for hemostasis; this level is easily attained with FFP.

(continued)

<table>
<thead>
<tr>
<th>Table 4 – Managing severe bleeding in patients with cirrhosis</th>
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<tbody>
<tr>
<td>- Monitor coagulation parameters (particularly prothrombin time [PT], platelet count, and fibrinogen level).</td>
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<td>- Localize the site of bleeding (for example, esophageal varices) to provide definitive therapy.</td>
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<tr>
<td>- Administer red cells and platelets as indicated by blood counts. Maintain platelet counts above approximately 80,000/μL.</td>
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<tr>
<td>- Administer vitamin K (2 mg intravenously) at the start of therapy.</td>
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<tr>
<td>- If the PT is prolonged (1.5 times control), administer fresh frozen plasma (FFP) as soon as possible. One protocol suggests that a minimum infusion of 1,200 mL (6 units) is required to reduce the PT to within three seconds of normal; if the PT is more than 20 seconds, 10 units of FFP should be infused initially.</td>
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<tr>
<td>- If the fibrinogen level remains low (below 100 mg/dL), transfuse cryoprecipitate (1 bag per 3 kg of body weight).</td>
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Reversal of warfarin effect

Patients who are anticoagulated with warfarin are deficient in the functional vitamin K–dependent coagulation factors II, VII, IX, X, as well as the anticoagulant proteins C and S. In a patient who has mild bleeding or who is preparing for elective surgery, intravenous vitamin K reduces warfarin effect within four to 12 hours. In the mildly bleeding patient, a low intravenous dose of vitamin K (10 mg) usually stops bleeding without totally removing the protective effects of anticoagulation.

When bleeding is life-threatening or emergency surgery is needed, 4 to 5 units of FFP should be transfused immediately, and 25 to 30 mg of intravenous vitamin K should be given to completely reverse the warfarin effect. An alternative therapy is factor IX concentrate (prothrombin complex), which contains factors II, VII, IX, and X. However, thrombosis is sometimes associated with this preparation, as is a risk of viral disease transmission, although the recent addition of virus inactivation steps has made these preparations much safer. (Disease transmission during transfusion therapy will be discussed in a coming issue of *The Journal of Critical Illness*.)

Disseminated intravascular coagulation

DIC can occur in numerous settings, including sepsis, shock, malignancy, and leukemia. It may also develop following a hemolytic transfusion reaction or as a complication of pregnancy. Prolonged PT, reduced levels of platelets and fibrinogen (the latter is usually below 100 mg/dL), and elevated levels of fibrin split products are characteristic findings.

Management of DIC remains controversial. In general, however, neither plasma products nor platelets should be administered unless the patient is bleeding.

One suggested protocol for the patient with DIC and massive bleeding includes:
- Management of causative factors that precipitate DIC.
- Administration of platelets (10 units).
- Administration of FFP (4 to 6 units).
- Use of cryoprecipitate if hypofibrinogenemia is present.

Consultation with a hematologist is the most prudent course.

Antithrombin III deficiency

The NIH consensus panel advocates the use of FFP as a source of antithrombin III for patients deficient in this inhibitor who must either undergo surgery or receive heparin for thrombosis. (Antithrombin III will be discussed in detail in our next article.)

TTP

Thrombotic thrombocytopenic purpura (TTP) is a potentially catastrophic disease characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, fever, renal disease, and neurologic dysfunction. Proposed pathologic mechanisms include:
- Production of antiplatelet and antithrombolytic antibodies leading to in vivo platelet aggregation.
- Deficiency of a compound that stimulates production of vessel wall prostacyclin.
- The formation of high molecular weight von Willebrand multimers that spontaneously aggregate platelets.

The therapy of choice is plasma exchange transfusion with FFP replacement or infusion of large
Best use of plasma components, Part 1: Fresh frozen plasma

amounts of FFP. The proposed effect of plasma is either to supply a factor missing in patients with TTP or to neutralize a noxious substance that is present. Various other therapies—such as corticosteroids, antiplatelet agents, intravenous γ-globulin, and vincristine—have been proposed.

[Editor's note: Drs. Huff and Kickler will discuss the role of plasma derivatives (cryoprecipitate, intravenous immune globulin, albumin solutions, fibrinectin, and antithrombin III) in a coming issue of The Journal of Critical Illness.]

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Glaxo

ZANTAC injection in vials

Glaxo Inc., Research Triangle Park, NC 27709

Glaxo injection in prefilled syringes

Manufactured for Glaxo Inc., Research Triangle Park, NC 27709
by Serumm Technology, Inc., Bethesda, MD 20814

ZANTAC Injection Premix

Glaxo Inc., Research Triangle Park, NC 27709

Manufactured by Abbott Laboratories, North Chicago, IL 60064

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