# Plasma

## How Supplied:

*Fresh Frozen Plasma (FFP) or Plasma Frozen Within 24 Hours After Phlebotomy (PF24)*

- Plasma prepared from either a whole blood or apheresis collection and frozen within 8 hours (FFP) or 24 hours (PF24) of collection
- FFP and PF24 once thawed are stored at 1-6°C for 24 hours unless converted and relabeled as *Thawed Plasma*
- Contain similar levels of clotting factors and can be used interchangeably[1]
- Volume is specified on product label and generally ranges from 200-310 mL

*Thawed Plasma*

- Unit of FFP or PF24 that ***is thawed at hospital*** *a*nd then relabeled as *Thawed Plasma*
- Stored at 1-6°C for up to 5 days from date FFP or PF24 thawed
- Use is determined by individual hospital policy
- Considered therapeutically equivalent to FFP/PF24[1]

*Plasma Cryoprecipitate Reduced*

- Prepared from FFP (*not PF24*) after cryoprecipitate is removed
- Once thawed, store at 1-6°C for 24 hours; unless relabeled as *Thawed Plasma Cryoprecipitate Reduced* and then may be stored for up to 5 days from date product thawed[1]
- Contains limited levels of factor VIII, factor XIII, vWF, fibrinogen, and fibronectin
- Indicated for use in the treatment of thrombotic thrombocytopenic purpura (TTP)
- Should not be used as a substitute for FFP, PF24 or thawed plasma[1]

*Liquid Plasma*

- Plasma prepared from a whole blood collection which is stored at 1 to 6°C (never frozen)
- Specifically approved for patients undergoing massive transfusion because of life-threatening hemorrhage and who have clinically significant coagulation deficiencies
- Liquid plasma should be used within 21 days from collection to provide clinically appropriate coagulation[2,3]
- Component is irradiated prior to distribution from Versiti since it contains viable lymphocytes and can theoretically cause transfusion-associated graft-versus-host disease (TA-GVHD) in susceptible individuals
- Liquid plasma is a "**special order**" and requires coordination with Versiti. All requests must be coordinated with your Hospital Relations Specialist.

## Utilization Review Guidelines:

Plasma transfusion therapy is indicated for treatment of coagulopathy attributable to coagulation factor deficiency where it is expected that replacement with plasma transfusion is the most efficient way to

correct that deficiency. Documentation of the indication(s) for a transfusion episode and special circumstances for transfusion that take place outside these guidelines is recommended.

## Best Practice:

- Abnormal coagulation test results ***do not*** predict the risk of bleeding during invasive procedures. Transfusion of plasma prior to a procedure for correction of mildly elevated test results neither corrects the abnormality nor reduces the perceived bleeding risk.[4-6]
- If medically necessary, transfuse plasma no sooner than 5 to 6 hours prior to a procedure for maximum effect.
- Plasma should not be used for reversal of vitamin K antagonists in patients without severe bleeding.[7-11]

## Indications:

1. Active bleeding ***and*** documented coagulopathy (INR ≥1.8 or PT and/or aPTT greater than 1.5 times upper limit of normal range). Common settings include:
    - Liver disease with coagulopathy
    - Emergent/urgent reversal of warfarin effect when Prothrombin Complex Concentrate (PCC) is not available
    - Disseminated Intravascular Coagulopathy (DIC)
        - Evaluate for hypofibrinogenemia; consider administration of cryoprecipitate
    - Dilutional coagulopathy/surgical bleeding
        - Best guided by timely coagulation testing
        - With massive transfusion and damage control resuscitation for trauma patients, early and balanced use of plasma (e.g. RBC:FFP ratio 1:1 to 2:1) is recommended.[12]
    - Replacement of single factor deficiencies for which no single factor concentrate product is available (e.g. factor XI or V deficiency)
2. Prophylaxis in patients undergoing surgery or invasive procedure and documented coagulopathy (INR ≥1.8; PT or aPTT greater than 1.5 times upper limit of normal range).
3. Replacement fluid in therapeutic plasma exchange (TPE) when bleeding or additional bleeding risks are present.
4. Treatment of thrombotic thrombocytopenic purpura (TTP):
    - FFP/PF24, Thawed Plasma and cryo-poor plasma are all acceptable products
5. Treatment of patients who have acute onset of angioedema related to ACE inhibitors or in hereditary angioedema (C1 esterase inhibitor deficiency) and who are refractory to standard of care.[13,14]

## Dosing Recommendations:

- Dose of 10-20 mL/kg body weight will typically provide appropriate procoagulant factors.
- Transfusion of a single unit of plasma for an average sized adult is inadequate for the replacement of coagulation factors.
- Factor levels in donor plasma are variable but can be assumed to be approximately 1 U/mL or 1%/mL.

## Expected Outcomes:

1. Each dose (10-20 mL/kg) increases patient's coagulation factor levels by 30-40%. Coagulation factor levels of approximately 30% are required for hemostasis.
2. Post-transfusion recovery of transfused factors may be less than expected due to extravascular distribution or consumption.

## Comments:

- Recommendation for patients on warfarin[7,8]

  Elevated INR Without Bleeding
  - Plasma is not indicated in these clinical situations.
  - Holding or lowering of next warfarin dose is generally effective.
  - Vitamin K (low dose) may be indicated based on degree of INR elevation.

  Elevated INR With Major Bleeding[15-17]
  - Co-administration of 4-factor Prothrombin Complex Concentrate (4-F PCC; e.g. Kcentra®) and slow IV infusion of Vitamin K should be considered.
  - 4-F PCC is preferred to FFP because the coagulopathy correction will be significantly faster.

  Elevated INR and Invasive Procedure/Surgical Patients[18-20]
  - For Non-Urgent Surgical Procedures:
    - Holding warfarin and/or use of Vitamin K should be considered based on timing of surgical procedure.
  - For Urgent/Emergent Procedures:
    - If the procedure will occur within 6 hours, plasma or 4-F PCC to replace clotting factors and help control bleeding is recommended. If sustained reversal is needed Vitamin K must be administered.
    - If procedure will occur after 6-24 hours, Vitamin K should be considered as first line treatment. Preferred routes of Vitamin K are oral or IV. Full effect can be seen in 6-12 hours with IV or in 24 hours with oral route. Subcutaneous Vitamin K should not be used because of erratic absorption.[17,20,21]

- Interventional Radiology (IR) procedure considerations[22]
  - Consider use of an algorithm to assess patients on anticoagulant therapy and needing IR procedure:
    - Assess bleeding risk of procedure and patient.
    - Is procedure emergent?
    - Does patient have high thrombotic risk? Consider bridge therapy.
    - If emergent with high risk of bleeding, consider reversal of anticoagulant.
  - For low bleeding risk procedures (e.g. non-tunneled or tunneled venous catheter placement and removal, paracentesis, thoracentesis), the following parameters are recommended:
    - Correct INR to range within ≤2.0-3.0
    - Correct platelet count to >20,000/µL

    - For high bleeding risk procedures (e.g. solid organ biopsies, gastrostomy or gastrojejunostomy tube placement, epidural injections, nephrostomy tube placement, transjugular intrahepatic shunt placement), the following parameters are recommended:
        - Correct INR to range within ≤1.5-1.8
        - Correct platelet count to >50,000/µL

- Most studies to date have failed to show a relationship between preprocedural mild to moderate abnormal coagulation tests and increased bleeding complications in patients undergoing interventional radiology (IR) procedures. In a single center retrospective study, the use of prophylactic plasma transfusion prior to invasive IR procedures in patients with INR ≥1.5 was not associated with decreased RBC transfusion rates or improved patient outcomes.[23]

- Plasma therapy is not indicated for a mildly elevated INR value, or if given will not bring the INR into the normal reference range in such cases.[24] For an elevated INR (i.e. <1.8), treat underlying condition and provide supportive care including use of Vitamin K in the settings of warfarin therapy or Vitamin K deficiency.

- Plasma products are not indicated for volume expansion, nutritional supplementation, or if the PT/INR and aPTT are normal.[1]

- Given the complex coagulopathy in liver disease, the commonly utilized thresholds for INR do not correlate with bleeding risk and should not be used. In patients with cirrhosis or advanced liver disease with an elevated INR, transfusion of plasma (and platelets) prior to low-risk therapeutic procedures (e.g. paracentesis, thoracentesis and routine endoscopic variceal band ligation) is generally not indicated. For management of active bleeding or high-risk procedures, transfusions to maintain hematocrit ≥25%, platelet count >50,000/µL, and fibrinogen >120 mg/dL may better optimize clot formation.[25]

- During resuscitation for massively bleeding trauma patients, a high transfusion ratio of RBC to plasma (1:1 or 2:1) and earlier administration of plasma has been found to improve outcomes; however, once stabilized, individualized component therapy based on laboratory or point-of-care testing is preferable over massive transfusion protocols.[26-28]

- Plasma products should not be used to reverse unfractionated Heparin or Low Molecular Weight Heparin (LMWH). Protamine is recommended for reversal of unfractionated heparin. While not fully effective (60% reversal), protamine is recommended for bleeding patients on LMWH.[17]

- Plasma will not reverse the direct oral anticoagulants (i.e. dabigatran, rivaroxaban, apixaban or edoxaban).[17] Antidotes for direct oral anticoagulants are available. See **Factor Concentrate Products** section for additional information.

- Isolated prolongation of aPTT is not an indication for plasma transfusion unless there is a known coagulation protein deficiency and the presence of bleeding or impending invasive procedure.

 

The most common causes of an isolated prolonged aPTT include heparin, lupus anticoagulants, factor VIII and IX deficiencies, and factor XII deficiency. In these clinical settings, plasma transfusion is not indicated.

- Liquid Plasma should not be used as the treatment for coagulation factor deficiencies when plasma products with higher clotting factor concentrations are available.[1] More information on the use of Liquid Plasma can be found in *TxMD ™ Choosing Plasma for Massively Bleeding Patients*.
- For addition information on best practices for plasma transfusion see *TxMD ™ Myths and Realities of Plasma Use*.

## References:


1. AABB, America's Blood Centers, Armed Services Blood Program. Circular of information for the use of human blood and blood components. October 2017.
2. Backholer L, Green L, Huish S, et al. A paired comparison of thawed and liquid plasma. *Transfusion* 2017 Apr;57(4):881-889.
3. Gosselin RC, Marshall C, Dwyre DM, et al. Coagulation profile of liquid-state plasma. *Transfusion* 2013 Mar;53(3):579-590.
4. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidenced-based review. *Transfusion* 2005 Sep;45(9):1413-1425.
5. Muller MC, Arbous MS, Spoelstra-de Man AM, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial. *Transfusion* 2015 Jan;55(1):26-35.
6. Holland L, Sarode R. Should plasma be transfused prophylactically before invasive procedure? *Curr Opin Hematol* 2006;13:447-451.
7. Holbrook A. Schulman S, Witt DM, et al. Evidence-Based Management of Anticoagulant Therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 Feb;141(2 Suppl):e152S–e184S.
8. Tran HA, Chunilal SD, Harper PL, et al. An update of consensus guidelines for warfarin reversal. *Med J Aust* 2013 Mar 4;198(4):198-9.
9. Choosing Wisely, AABB, Five Things Physicians and Patients Should Question (#3). Released April 24, 2014. https://www.aabb.org/docs/default-source/default-document-library/resources/choosing-wisely-five-things-physicians-and-patients-should-question.pdf
10. Choosing Wisely, American Society of Clinical Pathology, Thirty Things Physicians and Patients Should Question (#22). Released September 25, 2018 (21-25). https://www.choosingwisely.org/wp-content/uploads/2015/02/ASCP-Choosing-Wisely-List.pdf
11. Choosing Wisely, American Society of Hematology, Fifteen Things Physicians and Patients Should Question (#4). Released December 4, 2013 (items 1-5), December 3, 2014 (items 6-10), and December 2, 2015 (Non-ASH recommendations). https://www.hematology.org/education/clinicians/guidelines-and-quality-care/choosing-wisely#list
12. Holcomb JB, Tilley BC, Baraniuck S, et al. Transfusion of plasma, platelets and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. *JAMA* 2015 Feb 3;313(5):471-482.
13. Karim MY, Masood A. Fresh frozen plasma as a treatment for life-threatening ACE-inhibitor angioedema. *J Allergy Clin Immunol* 2002 Feb;109(2):370-1.
14. Tang R, Chen S. Fresh frozen plasma for treatment of hereditary angioedema acute attacks. *Chin Med Sci J* 2012 Jun;27(2):92-95.
15. Kcentra (Package Insert) Kankakee, IL: CSL Behring LLC, Revised October 2018.
16. Lin Y, Callum J. Emergency reversal of warfarin anticoagulation. *CMAJ* 2010 Dec 14;182(18):2004.


 

17. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol* 2017 Dec 19;70(24):3042-67.
18. Burbury KL, Milner A, Snooks B, et al. Short-term warfarin reversal for elective surgery – using low-dose intravenous vitamin K: safe, reliable and convenient. *Br J Haematol* 2011 Sep;154(5):626–634.
19. Meehan R, Tavares M, Sweeney J. Clinical experience with oral versus intravenous vitamin K for warfarin reversal. *Transfusion* 2013;53(3):491-498.
20. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the anticoagulant forum. *Am J Hematol* 2019 Jun:94(6):697-709.
21. Polito NB, Kanouse E, Jones CMC, et al. Effect of vitamin K administration on rate of reversal. *Transfusion* 2019;59:1202-1208.
22. Patel IJ, Rahim S, Davidson JC, et al. Society of Interventional Radiology Consensus Guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions—Part II: Recommendations. *J Vasc Interv Radiol* 2019 Aug;30(8):1168–1184.e1.
23. Warner MA, Woodrum DA, Hanson AC, et al. Prophylactic plasma transfusion prior to interventional radiology procedures Is not associated with reduced bleeding complications. *Mayo Clin Proc* 2016 Aug;91(8):1045–1055.
24. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion* 2006 Aug;46(8):1279-1285.
25. O'Leary JG, Greenberg CS, Patton HM, et al. AGA Clinical Practice Update: Coagulation in cirrhosis. *Gastroenterology* 2019 Jul;157(1):34–43.e1.
26. Apfelbaum JL (Committee Chair), et al. Practice Guidelines for Perioperative Blood Management: An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiolo*gy 2015:122(2):241-275.
27. Spahn D, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):R76. Published 2013 Apr 19. doi:10.1186/cc12685
28. American College of Surgeons TQIP for Massive Transfusion in Trauma Guidelines. Released 2014.

## Additional Resources:

29. Kuramatsu JB, Sebill JA, Huttner HB. Reversal of oral anticoagulation in patients with acute intracerebral hemorrhage. *Crit Care* **23,** 206 (2019). *https://doi.org/10.1186/s13054-019-2492-8*
30. Huber J, Stanworth SJ, Doree C, et al. Prophylactic plasma transfusion for patients without inherited bleeding disorders or anticoagulant use undergoing non-cardiac surgery or invasive procedures. *Cochrane Database Syst Rev* 2019 Nov 28;11(11):CD012745. doi: 10.1002/14651858.CD012745.pub2
31. Goodnough LT, Shander A. How we treat management of warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood* 2011 Jun 9;117(23):6091-6099.

 