Overview

The purpose of this 3rd edition of the adult blood transfusion guidelines is:

1. To provide practitioners and caregivers with an overview of evidence-based, best practices for the appropriate use of blood and blood components in adult patients and thereby to promote optimal transfusion therapy.

2. To provide findings from recent randomized controlled trials and up to date references to support these practices. Selected references are listed under each section.

3. To provide guidance for development of indications for computer provider order entry (CPOE) transfusion order sets and/or establish audit criteria for review of blood ordering practice by the hospital transfusion committee or quality improvement committee.

The physicians and staff of the BloodCenter of Wisconsin’s Medical Science Institute (MSI) have compiled these guidelines after critical review of the cited references to provide practitioners with a comprehensive summary of the literature and society recommendations applicable to the indications for transfusion of blood components and factor concentrates in adults. Information and recommendations provided reflect the current scientific and clinical knowledge at the time of publication, are only current as of their publication date, and are subject to change without notice as advances emerge. For guidelines pertaining to neonates and pediatric patients, the reader should refer to BloodCenter of Wisconsin Pediatric Transfusion Guidelines (2015). The BloodCenter of Wisconsin Medical Advisory Committee completed review and final approval of these guidelines on July 29, 2015.

The MSI physicians hope to foster adoption of best practice for usage of blood and blood component by providing this guidance to each institution. This guidance is intended for educational and informational purposes only. Updates to these guidelines will be done in as timely a fashion as possible when new evidence-based practice becomes available. BloodCenter of Wisconsin (BCW) does not approve or endorse any specific methods, practices, or sources of information. BCW assumes no liability for any injury and/or damage to persons or property arising out of or related to the use of or reliance on any guidance document published by BCW.

Each institution’s medical staff in collaboration with their transfusion service medical director should review these guidelines. After review and acceptance by the institution’s respective Medical Executive Committee, the institution’s guidelines should be shared with all physicians and other practitioners who order blood and blood components. In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guidance.

These adult guidelines are recommendations only. These recommendations should not be construed as dictating an exclusive course of management, treatment or care, nor does the use of such recommendations guarantee a particular outcome. This guidance is not intended to replace a practitioner’s best judgment based on the clinical circumstances of a particular patient or patient population. The decision to transfuse or not to transfuse should be made by the patient’s physician only after a careful assessment of the patient’s clinical condition and laboratory parameters. Documentation for transfusion of all blood, blood components, and factor concentrates should include the indication(s) for the transfusion or infusion; this is especially important if the circumstances/indication for the transfusion falls outside established guidelines for the institution.
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Red Blood Cells

**How Supplied:** All Red Blood Cell products for adult transfusion supplied by BloodCenter of Wisconsin are leukocyte-reduced and the majority are suspended in Adsol additive with 42-day expiration from collection. Each unit is approximately 300-350 mL.

**Utilization Review Guidelines:**
Red blood cell (RBC) transfusion may be appropriate to improve oxygen carrying capacity. Documentation of the indication(s) for transfusion and special circumstances for transfusion that take place outside these guidelines is recommended.

**Best Practice:**
- Decision to transfuse should be based on **clinical assessment of the patient**, not solely on Hemoglobin (Hgb) or Hematocrit (Hct) value.¹
- When indicated, **single unit RBC transfusions** should be the standard for non-bleeding, hospitalized patients.¹
- A restrictive or lower transfusion threshold (Hgb 7-8 g/dL) is safe and indicated for most clinical scenarios.

**Indications:**
1. General
   - Hgb less than 7 g/dL: RBC transfusion usually indicated
   - Hgb 10 g/dL or higher: RBC transfusion usually not indicated
2. Active Bleeding (surgical or traumatic)
   - Acute blood loss of 30% or more of blood volume
   - Hemodynamic instability and/or signs/symptoms of anemia or tissue hypoxia (tachycardia, hypotension, or mixed venous oxygen saturation <55%) unresponsive to other measures and anticipated on-going bleeding
   - Target Hgb concentrations:
     - ≥7 g/dL in otherwise healthy patients
     - >8 g/dL in elderly patients and those with known cardiac or respiratory disease
3. Non-bleeding, Medical or Surgical Hospitalized Patients (See comments)
   - Critically ill (ICU) patients, including those with septic shock: Hgb threshold ≤7 g/dL²,³
   - Patients with upper gastrointestinal bleeding who are not in hypovolemic shock: Hgb threshold ≤7 g/dL⁴
   - Post-operative general, cardiac and orthopedic surgical patients who are asymptomatic and not bleeding: Hgb threshold ≤8 g/dL⁵,⁶,⁷ (See comments)
   - Hemodynamically stable patients with pre-existing cardiovascular disease: Hgb threshold ≤8 g/dL⁵
   - Patients with acute coronary syndrome (acute MI, unstable angina) have lower tolerance for anemia; they may require a higher Hgb threshold (9-10 g/dL)⁸
   - Patients with traumatic brain injury, subarachnoid hemorrhage, or evidence of cerebral ischemia may require higher Hgb thresholds (~9 g/dL)⁸,⁹
4. Symptomatic anemia in a normovolemic patient with Hgb <10 g/dL, regardless of Hgb level.¹⁰
5. Perioperative Surgical Patients
   - **Prior to elective surgical procedures**, patients should be evaluated for anemia and appropriate management initiated (e.g., iron replacement for iron deficiency) in order to optimize the patient for best outcomes.\(^{11}\)
   - Determination of whether Hgb concentration between 6-10 g/dL justify or require RBC transfusion should be based on potential or actual ongoing bleeding (rate and magnitude), intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve.\(^{11}\)

6. Special Patient Situations
   - Outpatients with bone marrow failure may be prophylactically transfused to maintain Hgb >7g/dL. Transfusions are almost never indicated when Hgb ≥10 g/dL.
   - For patients with sickle cell disease prior to undergoing major surgical procedure: RBC transfusions to increase Hgb to 10 g/dL is recommended.\(^{12}\)

**Dosing Recommendations:**
- One unit of red cells should raise the Hgb on average 1 g/dL or Hct 3% in a 70-80 kg adult.
- In non-actively bleeding patients, assessment of post transfusion Hgb may be done as early as 15 minutes after completion of the transfusion and is equivalent to one drawn at 1 hour and 24 hours following the transfusion.\(^{13}\)

**Comments:**
- No single criterion should be used as an indication for RBC transfusion. Multiple factors related to patient’s clinical status and oxygen delivery should be considered.
- RBC transfusions should be performed only after appropriate alternative therapies have been considered (e.g. iron, vitamin B12, folate and erythropoietin).\(^{14}\)
- Restrictive transfusion strategy (defined as setting lower thresholds for initiating a transfusion and transfusing to lower targets than previously accepted) has been shown to be safe in most clinical settings. Use of a restrictive transfusion threshold in critically ill patients (including those with sepsis), surgical patients (cardiac and orthopedic), and patients with gastrointestinal bleeding has been shown to reduce transfusion rates without increasing morbidity or mortality. Meta-analysis of the several randomized control trials comparing restrictive versus liberal transfusion thresholds for hospitalized and surgical patients found reduction in cardiac, neurologic, and pulmonary complications, shorter length of stay and decreased infection rates in the restrictive transfusion group.\(^{15,16,17}\)
- Adherence to a restrictive transfusion threshold of Hgb 7 g/dL and thereby fewer blood transfusions may benefit some patients with upper GI bleeding. Lower portal venous pressure and subsequent fewer re-bleeding episodes have been hypothesized to explain the improved outcomes in the patients undergoing a restrictive transfusion strategy compared to liberal strategy. Patients with hypotension due to severe bleeding and patients with cardiovascular disease may need to be transfused at a higher Hgb threshold. Transfusion decisions in patients with upper GI bleeding and hypovolemic...
shock should be based on hemodynamic status, co-morbidities, and rate of bleeding with transfusions occurring prior to the Hgb reaching 7 g/dL.\textsuperscript{4,18}

- Certain surgical patients in the immediate postoperative period may benefit from a higher Hgb threshold. For surgical oncology patients who undergo major abdominal cancer surgery a liberal transfusion threshold (Hgb <9 g/dL) may be associated with fewer postoperative complications and lower risk for all-cause mortality.\textsuperscript{7} Higher Hgb threshold is also suggested for postop cardiac patients when there is evidence of ongoing bleeding, end-organ ischemia, hypotension not responding to low-dose pressors, and when unable to increase mixed venous saturation over 50% by increasing cardiac output safely.\textsuperscript{6,19}

- Studies done in postoperative surgical patient population have shown increases in morbidity starting with Hgb <7 g/dL, and significantly increased when Hgb <6 g/dL.\textsuperscript{20}

- Observational studies of RBC transfusion in acute coronary syndrome seem to favor a restrictive transfusion strategy; however, these observational studies are often confounded by patients who receive more blood transfusion and are sicker than those who do not. Two small randomized controlled trials comparing transfusion triggers of 8 and 10 g/dL in anemic patients with acute coronary syndrome showed conflicting results. In one trial a higher incidence of worse outcome was seen in the liberal strategy whereas the second trial showed a trend toward fewer major cardiac events and death in the liberal strategy group. The results from these trials support the need for a large randomized control trial (RCT) in this patient population.\textsuperscript{21,22,23}

- Results from studies involving general critical care patients should not be extrapolated to patients with subarachnoid hemorrhage, acute ischemic stroke, or traumatic brain injury. It is felt that these neurocritical patients are particularly vulnerable to secondary insults such as anemia and also the acutely injured brain may not tolerate a decrease in oxygen delivery as compared to other end-organ vascular beds. Some observational data suggest that acute brain injury patients may benefit from RBC transfusion and a higher hemoglobin trigger of 9 g/dL; however, large randomized trials are needed to provide best practice for transfusions in this patient population.\textsuperscript{8}

- In patients with chronic anemia who are unresponsive to iron replacement and/or ESA (erythropoiesis stimulating agents) therapy or patients with hemoglobinopathies (i.e. sickle cell anemia), the decision for transfusion should be individualized and determined by the patient’s symptoms caused by the anemia, rather than an arbitrary Hgb threshold.

- The optimal transfusion threshold for ambulatory patients has not been established. Utilizing evidence from inpatient trials, transfusions are generally not indicated when Hgb >10 g/dL; indicated when Hgb <7 g/dL in otherwise healthy adults; and indicated when Hgb <8 g/dL in patients with pre-existing cardiovascular disease.

- Regardless of Hgb level, RBC transfusions may be appropriate if any of the following are present: organ ischemia; increased potential for or ongoing blood loss; and symptoms of anemia including myocardial ischemia, orthostatic hypotension or tachycardia unresponsive to fluid replacement.
• Limitations of recommendations and where additional studies are needed:
  o Acute coronary syndrome/unstable angina/heart failure
  o Patients with lower gastrointestinal bleeding
  o Patients with coagulopathy and/or hemorrhagic shock
  o Patients with traumatic brain injury/subarachnoid hemorrhage/stroke
  o Patients with cancer and other oncological conditions

WHOLE BLOOD (WB):
• How supplied: 1 unit contains approximately 550 mL; all whole blood units are leukocyte-reduced. WB units must be ABO identical.
  o Availability of whole blood is limited in this community.
• Indications: Institution and patient specific. When available, indicated for those who require oxygen carrying capacity and have large volume deficit (e.g. massively bleeding patients, during liver transplantation).

References:
11. Apfelbaum JL (Committee Chair) et al. Revised by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Practice Guidelines for Perioperative Blood Management: an Updated Report by


**Additional Resources:**


Autologous and Directed Units – General Comments

**Autologous Blood Usage:**

Preoperative autologous blood donation (PAD) is no longer a standard of care for routine surgical patients.

Use of PAD may be indicated for patients where blood availability is limited, such as:

- Patients with multiple RBC alloantibodies or when provision of appropriate antigen negative, crossmatch-compatible RBC units are limited
- Patients who refuse allogeneic blood but will consent to PAD

**Autologous blood transfusion is not without risk and the criteria for transfusion of such products should be the same as that for allogeneic blood.** Though adverse reactions to autologous blood are minor (febrile and allergic symptoms) the frequency is similar to allogeneic blood transfusions. Other risks associated with autologous blood transfusions may include transfusion associated-bacterial contamination and incompatible transfusion due to misidentification at time of sample collection or administration. Errors related to production and handling of autologous units are not uncommon with one quarter of the errors related to autologous units not being available at the start of surgery, diminishing any benefit from the autologous collection.¹,²

**If Autologous Blood is being contemplated, CONSIDER:**

- Autologous units cannot be transfused to anyone other than the person who donated the unit as the criteria for donation of autologous blood is not the same as that for allogeneic, volunteer donors.
- Strong consideration should be given to the use of perioperative blood recovery and/or acute normovolemic hemodilution in place of preoperative autologous blood donation for surgical cases where blood transfusion may be likely.
- PAD should occur only when there is adequate time for replenishment of the red cells lost by the donation.
- Strong consideration should be given to use of iron replacement therapy, and possibly with erythropoiesis stimulating agents, to prevent pre-operative anemia that may develop as a result of preoperative autologous blood collection.
- See [www.bcw.edu](http://www.bcw.edu) for additional information about autologous blood donation. A physician order is required for autologous donation. Pre-surgical autologous donations must be made 8 or more days prior to date of surgery.
**Directed Donations:**

- Directed donations are blood donated by family or friends specifically for an individual.

- Donors must meet all the criteria for allogeneic blood donations which allow the units to be released into the general inventory if not needed by the patient.

- ABO group and Rh type of directed donations must be compatible with the patient; if not, the unit is released into general inventory.

- Directed donated units are not necessarily safer than those collected from volunteer donors.

- Directed donations intended for biological family members must be irradiated to prevent transfusion-transmitted Graft-versus-Host-Disease.

*If Direct Donation is being contemplated, CONSIDER:*

- A woman should not receive a transfusion from a man or his blood relatives if she has had or is planning to have his children.

- Transfusion from a woman to her biologic children or the father of her biologic children should be avoided. (Some women may possess antibodies developed during pregnancy that may result in a transfusion reaction in her child or child’s father.)

- See [www.bcw.edu](http://www.bcw.edu) for additional information about directed blood donation. A physician order is required for a directed donation. Such donations must be made at least 3 days, and preferably one week, prior to the expected transfusion.

**References:**


Platelets

How Supplied: Only leukocyte-reduced single donor apheresis platelets (SDP) are supplied by BloodCenter of Wisconsin. These SDP products are considered equivalent to 6 whole blood-derived platelets.

Utilization Review Guidelines:
Platelets are administered for the prevention or treatment of bleeding in patients with thrombocytopenia or platelet function defects. Documentation of the indication(s) for a transfusion episode and special circumstances for transfusion that take place outside these guidelines is recommended.

Best Practice:
- Prophylactic platelet transfusion in non-bleeding surgical patients with platelet count >50,000/µL is not recommended.
- When indicated, a single dose of platelets (one unit Apheresis Platelets) should be given followed by re-assessment for need of additional doses.¹

Indications:
1. Active bleeding and platelet count <50,000/µL or presumed/known platelet function defect
2. Prophylaxis treatment in hematology/oncology patients:¹⁻⁵
   - Platelet count <10,000/µL in stable patient
   - Platelet count <20,000/µL and presence of risk factor for bleeding (h/o bleeding, infection, Disseminated Intravascular Coagulopathy)
3. Surgical/invasive procedures:¹⁻⁶
   - Platelet count <50,000/µL for non-neuraxial surgery procedures with minimal bleeding risk
   - Platelet count <100,000/µL for CNS, eye, airway or other areas where there is high risk of microvascular bleeding
   - Presumed/known platelet function defect
   - Open heart surgery and cardiopulmonary bypass with perioperative bleeding and thrombocytopenia and/or platelet dysfunction
4. In the setting of massive transfusion support for patients who are massively bleeding and when platelet counts cannot be measured in a timely manner

Dosing Recommendations:
- Transfuse 1 unit of SDP and reassess to determine adequate rise in platelet count.
- Single unit of SDP generally raises platelet count by 30,000-50,000/µL in a 70 kg non-bleeding patient.

Comments:
- For patients on antiplatelet inhibitors with intracranial hemorrhage and a normal platelet count, the decision to transfuse platelets should be an individual clinical decision since the efficacy of such practice is unknown.⁷
• For patients on anticoagulation (e.g. heparin or target-specific oral anticoagulants), a platelet threshold of <50,000/µL for prophylaxis treatment may be considered.

• Platelet function defect should be documented by abnormal laboratory assessment of platelet function; or presumed due to medications that inhibit platelet function, hypothermia, or mechanical devices that affect platelet function.

• Recommendations for stopping medication prior to invasive procedures vary with the medication and clinical situation. Platelet function tests may help assess the level of platelet inhibition and timing of surgical procedure. Platelet replacement of 1-2 apheresis units is usually adequate to control bleeding.6,8,9

• No definite threshold for platelet count prior to central venous catheter insertion has been established. Recent retrospective studies indicate that patients with a pre-procedure platelet count <20,000/µL may benefit from platelet transfusion to reduce the incidence of bleeding.1,10

• In the PLADO trial11 no difference in bleeding outcomes was noted in adult hospitalized patients with hematologic malignancies undergoing chemotherapy or stem cell transplantation whether they received low-dose, standard-dose or high-dose platelet transfusions. The higher dose strategy provided no additional hemostatic benefit. Either low-dose or standard-dose platelet transfusion strategy is recommended for patients receiving myelosuppressive chemotherapy and requiring prophylactic platelet transfusions.1,3

• Two recent randomized controlled trials studied prophylactic (platelet count <10,000/µL) versus therapeutic (only when bleeding occurred) platelet transfusion strategy in patients with hematologic malignancies. While reduced platelet transfusions occurred in the therapeutic group, the incidence of bleeding was higher. These results support the continued use of prophylactic platelet transfusions in patients with hematologic malignancies receiving chemotherapy.12,13

• Consider the administration of DDAVP in addition to administration of platelets to control refractory bleeding in patients with uremia, cardiopulmonary bypass-induced platelet dysfunction,6,14 or type I von Willebrand disease.

• Platelet transfusion is generally contraindicated, unless there is a life-threatening bleed, in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia, and immune thrombocytopenia. Prophylactic platelet transfusions are generally not indicated for patients with chronic, stable, severe thrombocytopenia (i.e. aplastic anemia or myelodysplasia). Platelet transfusions for bleeding episodes are more appropriate.

• In patients with an inadequate rise in 1-hour post-transfusion platelet count and have HLA antibodies, HLA-matched platelets may be indicated.3
References:


Additional Resources:


Plasma

How Supplied:

**Fresh Frozen Plasma (FFP)/FP24**
- Plasma prepared from either a whole blood or apheresis collection and frozen either within 8 hours (FFP) or 24 hours (FP24) of collection
- FFP and FP24 can be used interchangeably
- Contains similar levels of clotting factors
- Volume is specified on product label and generally ranges from 200-325 mL

**Thawed Plasma**
- Unit of FFP or FP24 that was thawed and stored at 1-6°C for 1-5 days
- Use is determined by individual institutional policy
- Considered therapeutically equivalent to FFP/FP24

**Plasma Cryoprecipitate Reduced**
- Prepared from FFP (not FP24) after cryoprecipitate is removed
- Contains limited levels of factor VIII, factor XIII, vWF, fibrinogen, or fibronectin
- Indicated for use in the treatment of thrombotic thrombocytopenic purpura (TTP)

**Utilization Review Guidelines:**
Plasma transfusion therapy is indicated for treatment of documented coagulopathy, where the mechanism for coagulation defect is known, understood and attributable to coagulation factor deficiency and 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.\(^1\)\(^2\) Transfusion of plasma prior to a procedure for correction of mildly elevated test results neither corrects the abnormality nor reduces the perceived bleeding risk.\(^3\)
- If medically necessary, transfuse plasma no sooner than 5 to 6 hours prior to a procedure for maximum effect.
- In non-emergent settings, plasma should not be used for reversal of vitamin K antagonists.\(^4\)
Indications:
1. Active bleeding and documented coagulopathy (INR >1.7 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
   • Disseminated Intravascular Coagulopathy (DIC)
     a. Evaluate for hypofibrinogenemia; consider administration of cryoprecipitate
   • Dilutional coagulopathy/surgical bleeding
     a. Best guided by timely coagulation testing
     b. With massive transfusion and damage control resuscitation for trauma patients, earlier use of plasma (FFP:RBC ratio 1:1 – 1:2) is recommended. (See comments)
   • 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 >1.7; PT or aPTT greater than 1.5 times upper limit of normal range). (See comments)
3. Replacement fluid in therapeutic plasma exchange (TPE) when bleeding or additional bleeding risks are present.
4. Treatment of thrombotic thrombocytopenic purpura (TTP):
   • FFP/FP24, 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.

Dosing Recommendations:
• Dose of 10-20 mL/kg body weight typically raises procoagulant factors into hemostatic levels; monitor for desired outcome.
• Factor levels in donor plasma are variable, but can be assumed to be approximately 1 U/mL.
• Transfusion of a single unit of plasma for an average sized adult is considered under-dosing and is inadequate for the replacement of coagulation factors.

Outcome Indicators:
• Each dose (10-20 mL/kg) increases patient’s coagulation factor levels by 30-40%. Hemostasis usually requires coagulation factor levels of approximately 30%.
• Post-transfusion recovery of transfused factors may be less than expected due to extravascular distribution or consumption.
Comments:

- **Recommendation for patients on warfarin:**
  - **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 Bleeding:**
    - Co-administration of FFP and Vitamin K should be considered.
    - 4-factor Prothrombin Complex Concentrate (4-F PCC; e.g. Kcentra®) is available and preferred to FFP for life-threatening bleeding or intracranial hemorrhage because the rate of INR decrease will be significantly faster with 4-F PCC.\(^9\text{-}^{11}\)
  - **Invasive Procedure/Surgical Patients:**
    - For Non-Urgent Surgical Procedures:
      - Holding warfarin and/or use of Vitamin K should be considered based on timing of surgical procedure.\(^12\)
    - For Urgent/Emergent Procedures:
      - 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.\(^13,14\)
      - 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.

- Plasma therapy is generally not required for a mildly elevated INR value, nor will it bring the INR into the normal reference range.\(^15\) If INR is between 1.4-1.7, treat underlying condition and provide supportive care including use of Vitamin K in the settings of warfarin use or Vitamin K deficiency.

- Plasma will not reverse the target-specific oral anticoagulants (i.e. dabigatran, rivaroxaban, apixaban or edoxaban).

- Plasma products are not indicated for volume expansion, nutritional supplementation or if the PT/INR and aPTT are normal.\(^6\)

- Routine transfusion of plasma (and platelets) prior to abdominal paracentesis or endoscopic variceal band ligation in patients with cirrhosis is generally not indicated. Routine tests of coagulation do not reflect bleeding risk in patients with cirrhosis and bleeding complications in these procedures are rare.\(^16\)

- While high ratio of plasma to RBC and earlier administration of plasma has been found to improve outcomes in massively bleeding trauma patients,\(^5\) use of a 1:1 or 1:2 ratio (FFP:RBC) is not indicated when time allows for lab-directed component therapy.\(^17,18\)
• 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. Refer to institutional guidelines.

• Isolated prolonged aPTT is not an indication for plasma transfusion unless there is a known coagulation protein deficiency (with bleeding). 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.

References:


Additional Resources:


Cryoprecipitate AHF

How Supplied: Cryoprecipitate for adult transfusion is distributed as a pool of 5 units by BloodCenter of Wisconsin. Cryoprecipitated AHF contains factor VIII, von Willebrand factor, fibrinogen, factor XIII, and fibronectin.

Utilization Review Guidelines:
Cryoprecipitate is administered for the treatment of bleeding in patients with low or dysfunctional fibrinogen. Documentation of the indication(s) for a transfusion episode and special circumstances for transfusion that take place outside these guidelines is recommended.

Indications:
1. Hypofibrinogenemia (fibrinogen <125 mg/dL) with active bleeding or undergoing an invasive procedure
2. As part of a massive transfusion protocol for patients who are massively bleeding and fibrinogen cannot be measured in a timely manner
3. Obstetric patient with massive bleeding and fibrinogen <200 mg/dL (See comments)
4. Dysfibrinogenemia (acquired or congenital) with active bleeding or undergoing invasive procedure (See comments)
5. Replacement therapy in factor XIII deficiency with active bleeding or undergoing an invasive procedure when commercial factor concentrate is not available

Dosing Recommendations:
- 1 unit per 7-10 kg of body weight. For adults, one standard dose of cryoprecipitate is 10 units.
- ABO-compatible cryoprecipitate is not required in adults due to the small volume of plasma transfused. Rh compatibility need not be considered for transfusion.1

Outcome Indicators:
- 10 units (or two, 5-pool bags) in a 70 kg adult will typically raise the plasma fibrinogen levels by approximately 50-75 gm/dL.2 Monitor for desired outcome.

Comments:
- Fibrinogen threshold of 110-125 mg/dL is generally used; however, this value has not been rigorously defined in clinical trials.
- Studies show that fibrinogen under 200 mg/dL in pregnancy may be an independent risk factor for development of severe postpartum hemorrhage.3,4 Transfusion with cryoprecipitate may be preferable to FFP when attempting to rapidly control bleeding and regain hemostasis in an obstetric patient.5
- Cryoprecipitate transfusions are not generally indicated in the absence of bleeding.
- Use of cryoprecipitate in hemophilia A or von Willebrand disease (vWD) is NOT standard of care. Use targeted factor pharmaceuticals as first line therapy.
• Use of cryoprecipitate may be considered for control of uremic bleeding after other modalities have failed, but there is limited data to support routine use.\(^6\)

• Coagulopathy of liver disease is complex with multiple alterations in the hemostatic system (platelets, procoagulants and anticoagulants). In the absence of hypofibrinogenemia, cryoprecipitate may be indicated as an adjunct management with other clotting factors to help control bleeding in liver disease patients.

• In patients with congenital fibrinogen deficiency (afibrinogenemia, hypofibrinogenemia) with acute bleeding or impending surgery, consider fibrinogen concentrate (RiaSTAP\(^{®}\)) instead of cryoprecipitate.\(^7\)

• Congenital Factor XIII deficiency is rare and commercial Factor XIII concentrate (Corifact\(^{®}\)) is available for use in such patients.\(^8\)

• Historically, cryoprecipitate has been applied topically as part of an intraoperative “fibrin glue” in some specific surgeries. In current practice, commercially prepared fibrin sealants (e.g. Tisseel\(^{®}\), Evicel\(^{®}\)) are available; cryoprecipitate is rarely used for this purpose.\(^9\)

**References:**


**Additional Resources:**


Granulocytes

How Supplied: Granulocytes are collected from G-CSF-stimulated donors with a typical course consisting of 5 daily collections. Each unit collected contains on average 4-6x10^10 granulocytes.

- All requests for granulocytes are referred to a BloodCenter of Wisconsin physician for consultation with the ordering physician.

Utilization Review Guidelines:

Granulocytes can be administered for the treatment of severe neutropenia with the indications below. Documentation of the indication(s) for a transfusion episode and special circumstances for transfusion that take place outside these guidelines is recommended

Indications:

1. Severe neutropenia (absolute neutrophil count <500/µL) with reversible marrow hypoplasia and documented bacterial or fungal infection unresponsive to 48 hours of appropriate antibiotic therapy

2. Patients with severe neutrophil dysfunction and bacterial or fungal infection

Dosing Recommendations:

- Daily or every other day granulocyte transfusions are recommended until evidence of recovery indicated by:
  - Clinical resolution of infection
  - Neutrophil count >500/µL

Comments:

- Granulocytes must be irradiated before use.
- Granulocytes have a 24 hour shelf life but have best efficacy when transfused as soon as possible after collection.
- Generally not for use in patients in whom marrow recovery is not anticipated.
- Bedside leukoreduction filter should not be used during administration; use blood administration tubing with 170-260 micron filter
- Patients are highly likely to experience a transfusion reaction with granulocyte transfusion; premedication with acetaminophen and/or corticosteroids and slow infusion is suggested to mitigate adverse events.
- Granulocyte transfusion therapy remains controversial. There is clear evidence of no harm of transfusing granulocytes in the neutropenic population.
References:


Special Attributes

LEUKOCYTE-REDUCED BLOOD PRODUCTS (Red Blood Cells, Platelets)

All red cell and platelet products supplied by BloodCenter of Wisconsin are leukocyte-reduced including autologous whole blood/red cells.

Indications:
- Prevention of febrile non-hemolytic transfusion reactions
- Prevention of HLA alloimmunization to HLA antigens
- Prevention of cytomegalovirus infections in patients at risk for CMV transfusion-transmitted infection (Leukocyte-reduced products are considered ‘CMV-Safe’)

Comments:
- Guidelines from AABB require that a leukocyte-reduced blood product contain fewer than $5 \times 10^6$ leukocytes to prevent non-hemolytic febrile transfusion reactions, and for other indications.\(^1\) At BloodCenter of Wisconsin, both leukocyte-reduced red cells and leukocyte-reduced platelets generally contain <1x$10^6$ leukocytes.
- There is insufficient evidence of the role of leukocyte reduction in the prevention of transfusion-related immune modulation.

PHENOTYPED – MATCHED (Red Blood Cells)

Phenotypically matched red cell units are “matched” for the patient’s Rh and Kell antigens, regardless if the patient has the corresponding red cell antibodies or not. In patients who require chronic transfusions, providing phenotyped-matched blood has shown to decrease the rate of red cell alloimmunization from as high as 43% to only 2.2%.\(^2,3\)

Indications:
- Patients undergoing chronic transfusion therapy (i.e. sickle cell disease or thalassemia).

CYTOMEGALOVIRUS SERONEGATIVE (CMV NEGATIVE) CELLULAR PRODUCTS (Red Blood Cells, Platelets)

There is currently no definitive evidence to dispute the practice of using leukocyte-reduction alone as an effective means to reduce transfusion-transmitted CMV. Therefore, leukocyte-reduced blood need not be CMV seronegative to prevent recipient CMV seroconversion.\(^4-7\) The use of CMV seronegative should be based on availability and site-specific policies.

Indications:
- Newborns weighing <1500 grams
- Any intrauterine transfusion
- Allogeneic peripheral stem cell or bone marrow transplant patients or candidates who are CMV seronegative or of unknown CMV serostatus
- CMV seronegative bone marrow transplant donors who require homologous products
- Known or suspected congenital immunodeficiency due to T-cell defects (DiGeorge syndrome, etc.) or other severe immune deficiencies who are CMV seronegative
Potential Indications upon Physician Request:
- Pregnant women
- CMV seronegative patients with HIV
- Heart and lung transplant patients who are CMV seronegative
- CMV seronegative autologous stem cell transplant patients
- Any patient for whom the physician, in consultation with the Transfusion Service physician, determines may be at risk for serious post-transfusion CMV infection

Comments:
- ‘CMV Negative’ products are both leukocyte-reduced and serologically negative for CMV IgG.
- Leukocyte-reduced blood products are considered a safe alternative for CMV seronegative patients if CMV seronegative products are unavailable. Waiting for CMV seronegative blood products should not delay care.
- Some institutions or physicians may choose to use leukoreduction as the sole means of prevention of transfusion-transmitted CMV disease.\(^\text{4-7}\)
- CMV seronegative products are not required for patients who are CMV seropositive.
- CMV serostatus does not need to be considered for fresh frozen plasma or Cryoprecipitated AHF because these products are relatively acellular.
- Granulocyte transfusions, which are never leukocyte-reduced, should be CMV seronegative whenever possible when given to CMV seronegative patients.

IRRADIATED BLOOD PRODUCTS (Red Blood Cells, Platelets, Granulocytes)
Irradiated blood products are indicated for the prevention of transfusion-associated graft vs. host disease (TA-GVHD). Irradiated blood products are prepared by exposure of the blood component to gamma or X-ray irradiation.

Indications:
- Intrauterine transfusions
- Infants ≤12 months of age
- Donation from blood relatives
- HLA-matched platelets
- Granulocyte transfusions
- Recipients of allogeneic or autologous bone marrow/hematopoietic progenitor cell transplants.
- Patients with hematologic malignancies
- Patients with Hodgkin’s lymphoma
- Known or suspected congenital immunodeficiency due to T-cell defects (e.g. DiGeorge syndrome, SCID)
- Patients who have received purine analogue drugs (such as fludarabine, cladaribine, deoxycoformicin) or other related chemotherapeutic drugs
- Patients who are receiving alemtuzumab (anti-CD52 monoclonal antibody CAMPATH-1H),
- Aplastic anemia patients who are receiving anti-thymocyte globulin (rabbit derived) ATG medications.
• Patients with neoplastic disease considered to be at high risk for TA-GVHD by their physician

Comments:
• Irradiation of the product should be done as close as possible to the time of planned transfusion.
• Irradiation is not required for previously frozen products (FFP/FP24, Cryoprecipitated AHF).
• There is no indication for irradiation of red blood cells or platelets for patients who are HIV positive or have AIDS.
• Use of irradiated blood components is not routinely required for solid organ transplant patients.

WASHED (Red Blood Cells, Platelets)

Indications:
• History of anaphylactic reaction to blood components
• IgA deficiency with documented IgA antibody
• Recurrent severe allergic reactions not prevented with appropriate premedication
• Severe hyperkalemia (e.g. neonates)

Comments:
• To provide a washed product, the red cell or platelet unit is prepared using 0.9% sodium chloride. Washing removes plasma proteins, antibodies, potassium and free hemoglobin. There is loss of some red cells during the washing process. When preparing washed platelets, 20-30% of the platelets can be lost as well as loss of platelet function due to platelet activation.
• The expiration date of a washed red cell unit is 24 hours from the time the washing process commences.
• The expiration date of a washed platelet is 4 hours from the time the washing process commences.

References:


Factor Concentrates

Recombinant or plasma-derived Factor VIII (Helixate FS®)

In patients with moderate to severe factor VIII deficiency (hemophilia A) or with mild factor VIII deficiency unresponsive to DDAVP:

- Before and after an invasive procedure
- During and after acute bleeding and/or trauma
- For prevention of chronic joint disease
- Prophylaxis to prevent bleeding
- In patients with mild factor VIII deficiency responsive to DDAVP, when there is severe or life-threatening bleeding (such as intracranial hemorrhage) or high-risk surgery

Intermediate-purity plasma-derived Factor VIII (Humate-P®, Alphanate®, Wilate-Koate DVI®)

1. In patients with von Willebrand disease
   - Who are unresponsive to DDAVP:
     a. Before and after an invasive procedure
     b. During and after acute bleeding
   - For severe, life-threatening bleeding

2. Immune tolerance therapy in selected factor VIII-deficient patients with inhibitors (not Wilate-Koate DVI®)

Recombinant or plasma-derived Factor IX (BeneFIX®, Alprolix™, Rixubis)

In patients with factor IX deficiency (hemophilia B):

- Before and after an invasive procedure
- During and after acute bleeding and/or trauma
- For prevention of chronic joint disease
- Prophylaxis to prevent bleeding
- Immune tolerance therapy in factor IX-deficient patients with inhibitor (not Alprolix™ or Rixubis)

Activated Prothrombin Complex Concentrates (FEIBA)

- Bleeding episodes or surgical procedures in patients with hemophilia A or B with inhibitors
- Non-hemophiliac patients with acquired inhibitors to coagulation factors
- Possible use in dabigatran etexilate related bleeding (not FDA approved)

Recombinant Factor VIIa (rFVIIa, Novoseven®RT)

- Bleeding and surgical procedures in patients with factor VIII or IX deficiency and inhibitors
- Bleeding and surgical procedures in selected patients with congenital factor VII deficiency
- Bleeding in patients with acquired hemophilia
- Examples of non FDA-approved use include:
  a. Bleeding in patients with Glanzmann’s thrombasthenia
  b. Uncontrolled hemorrhage in on-pump cardiac surgery or extracorporeal membrane oxygenation (ECMO)
  c. Emergent reversal of warfarin
  d. Rescue therapy for trauma patients with massive transfusion
4-Factor Prothrombin Complex Concentrate (4-F PCC) (Kcentra®)
- Indicated for urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding or need for urgent surgery or other invasive procedure.
- Kcentra® is available as a single-use vial containing coagulation factors II, VII, IX and X, and antithrombotic Proteins C and S as a lyophilized concentrate.
- Dosing is based on INR results and body weight (see package insert; Table 1 below)
  - In patients with coagulopathy due to liver disease, 4-factor PCC may not be effective in controlling bleeding events.
  - Administration of Vitamin K is recommended in conjunction with Kcentra®.
  - Non FDA-approved use should be considered with caution and may include:
    - Protein S deficiency where no concentrate is available
    - Reversal of target-specific oral anticoagulants (TSOAC) such as rivaroxaban, apixaban or edoxaban
    - Treatment of other acquired factor deficiencies and trauma-induced coagulopathy

Table 1: Kcentra® dosing³

<table>
<thead>
<tr>
<th>Pre-Treatment INR</th>
<th>2 to &lt;4</th>
<th>4 to 6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Kcentra® (units of Factor IX / kg body weight)</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose (units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

3-Factor Prothrombin Complex Concentrate (3-F PCC) (Profilnine® SD)
- For urgent reversal of warfarin in life-threatening bleeding. Although this is an off-label indication, when 4-factor PCC is unavailable use of 3-factor PCC is recognized in such clinical situations and recommended by multiple practice guidelines.
- Example of non-FDA-approved use include: deficiency of other vitamin K-dependent factors in settings where no other concentrate is available (e.g. factor X and factor II deficiency)

Antithrombin III (AT III) Concentrate (ATryn®, Thrombate III))
- In patients with congenital antithrombin deficiency for:
  a. Prophylaxis for obstetric or surgical procedures
  b. Thromboembolism
- Non-FDA-approved use must be based on individual institutional policy. AT III has been used in patients with documented acquired antithrombin deficiency in:
  a. Venous or arterial thrombosis with associated heparin resistance
  b. Bone marrow transplantation with associated veno-occlusive disease
  c. Cardiopulmonary bypass or ECMO and heparin resistance
  d. Disseminated intravascular coagulation with severe AT deficiency
Fibrinogen Concentrate (Human; RiaSTAP®)
- Indicated for the treatment of acute bleeding in patients with congenital fibrinogen deficiency (CFD), including afibrinogenemia and hypofibrinogenemia.
- RiaSTAP® is not indicated for dysfibrinogenemia.

Protein C Concentrate (CEPROTIN-Human)
- Treatment of severe congenital Protein C deficiency for prevention and treatment of venous thrombosis and purpura fulminans
  - Can be used for adult and pediatric patients
  - Orphan drug status

C1 Esterase Inhibitor (Human; Berinert®)
- Treatment of ongoing, acute attacks of hereditary angioedema in adults and adolescents

Factor Concentrate Comments:
- Consultation with hematologist for treatment options and dosing is highly recommended.
- Any off label use of factor concentrates must be based on individual institutional policy.
- Antidotes for reversal of TSOAC agents are currently being developed and tested. Current recommendations for patients with bleeding on TSOACs include anticoagulation withdrawal, close monitoring, compression and/or local control of bleeding source, use of 4-factor PCC, and possible hemodialysis for dabigatran. Plasma will not reverse the effects of these newer oral anticoagulant medications.

References:


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# Summary of Thresholds for Blood Component Transfusion

Tables summarize conditions and thresholds for blood component transfusions based on laboratory values established as safe in clinical trials or from expert opinion (see respective section in Guidelines). These thresholds are not a substitute for direct assessment of the patient and clinical judgment. Clinical assessment may not support the need for transfusion in all patients.

## RED BLOOD CELLS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hgb Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized Patient</td>
<td></td>
</tr>
<tr>
<td>Active bleeding (acute blood loss ≥30%)</td>
<td>&gt;7g/dL</td>
</tr>
<tr>
<td>Critically ill in ICU (including sepsis)</td>
<td>≤7g/dL</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding (no shock)</td>
<td>≤7g/dL</td>
</tr>
<tr>
<td>Post-op surgery (including CV and ortho)</td>
<td>≤8g/dL</td>
</tr>
<tr>
<td>Hemodynamically stable pt w/cardiac disease</td>
<td>≤8g/dL</td>
</tr>
<tr>
<td>Acute MI, unstable angina</td>
<td>9-10g/dL</td>
</tr>
<tr>
<td>Traumatic brain injury, subarachnoid bleed</td>
<td>≤9g/dL</td>
</tr>
<tr>
<td>Symptomatic anemia in normovolemic patient (tachycardia, chest pain, hypotension)</td>
<td>&lt;10g/dL</td>
</tr>
<tr>
<td>Outpatient hematology/oncology patients</td>
<td>&gt;7g/dL</td>
</tr>
</tbody>
</table>

## PLATELETS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Platelet Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>&lt;50,000/μL</td>
</tr>
<tr>
<td>Prophylaxis in hematology/oncology patients</td>
<td>&lt;10,000/μL(stable); &lt;20,000/μL(with risk factors)</td>
</tr>
<tr>
<td>Surgery/Invasive procedure:</td>
<td></td>
</tr>
<tr>
<td>CNS, eye or other uncompressible site</td>
<td>&lt;100,000/μL</td>
</tr>
<tr>
<td>Other surgical procedures</td>
<td>&lt;50,000/μL</td>
</tr>
<tr>
<td>Known or presumed platelet function defect with bleeding or prior to procedure</td>
<td>Any platelet count</td>
</tr>
</tbody>
</table>

## PLASMA

<table>
<thead>
<tr>
<th>Condition</th>
<th>INR or aPTT Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>INR &gt;1.7 or aPTT &gt;1.5 times upper limit of normal</td>
</tr>
<tr>
<td>Prophylaxis prior to surgery/invasive procedure</td>
<td>INR &gt;1.7 or aPTT &gt;1.5 times upper limit of normal</td>
</tr>
<tr>
<td>Urgent reversal of warfarin (bleeding or prior to procedure)*</td>
<td>INR &gt;1.7</td>
</tr>
<tr>
<td>Treatment of TTP</td>
<td>N/A; INR not needed</td>
</tr>
<tr>
<td>Replacement fluid for TPE when bleeding risks</td>
<td>N/A; INR not needed</td>
</tr>
</tbody>
</table>

*when insufficient time for vitamin K to take effect (i.e. 6 hr for IV, 24 hrs for PO) or for life-threatening bleeding when PCC unavailable

## CRYOPRECIPITATE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Fibrinogen Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypofibrinogenemia with bleeding or undergoing invasive procedure</td>
<td>&lt;125 mg/dL</td>
</tr>
<tr>
<td>Post-partum massive bleeding</td>
<td>&lt;200 mg/dL</td>
</tr>
<tr>
<td>Dysfibrinogenemia with bleeding</td>
<td>Any fibrinogen level</td>
</tr>
</tbody>
</table>