BLOOD PRODUCT REPLACEMENT: OBSTETRIC HEMORRHAGE

Larry Shields, MD, Central Coast Maternal Fetal Medicine; Richard Lee, MD, Los Angeles County and University of Southern California Medical Center; Maurice Druzin, MD, Division of Maternal Fetal Medicine, Stanford University School of Medicine; Jennifer McNulty, MD, Division of Maternal Fetal Medicine, Long Beach Memorial Medical Center; Holli Mason, MD, Transfusion Medicine and Serology, Harbor UCLA Medical Center

BACKGROUND AND LITERATURE REVIEW

After the first several units of packed red blood cells (PRBCs) and in the face of continuing or worsening hemorrhage, aggressive transfusion therapy becomes critical. This report covers the new science of massive transfusion protocols. Lessons from military trauma units in Iraq as well as civilian experience with motor vehicle accidents and massive obstetric hemorrhage have identified new principles such as prominent use of fresh frozen plasma (FFP) and resuscitation transfusion without waiting for laboratory results.

Life-threatening maternal hemorrhage occurs in approximately 1-2% of deliveries and is a leading cause of maternal death in both industrial and developing countries. (1, 2) Delays in recognizing and treating hemorrhage frequently lead to inadequate blood product replacement and concomitant development of disseminated intravascular coagulation (DIC). Both of these factors significantly contribute to maternal morbidity and mortality. Furthermore, delayed treatment increases the likelihood that the patient will require multiple units of blood products and, if available, activation of “massive hemorrhage protocols.” This section reviews blood component replacement therapy in the context of significant maternal hemorrhage.

Nine massive hemorrhage protocols tailored specifically to obstetrics were evaluated. (1-9) No formal clinical trials were available and all of the protocols were developed in consultation with obstetric and hematology “experts.” Only one has published a case series of their results. (7) The salient feature of each protocol was an attempt to address three primary problems: 1) delayed diagnosis; 2) underestimated blood loss; and 3) treatment and prevention of fulminate disseminated intravascular coagulation (DIC). (9) To address these problems, the use of “obstetrical hemorrhage packs,” which included all needed blood components (i.e. PRBCs, FFP, cryoprecipitate, platelets) was recommended. None of the protocols recommended routine use of recombinant factor VIIa as part of initial therapy. The American College of Obstetrics and Gynecology has no specific recommendation for the use of blood components for treating postpartum hemorrhage. (10) Recommendations by the American Society of Anesthesiologists Task Force on Perioperative Blood Loss are consistent with the protocols reviewed here and with recommendations outlined below.
BLOOD PRODUCTS

PACKED RED BLOOD CELLS (PRBCs)
The majority of protocols recommended six units of PRBCs be prepared and available and hematocrit be maintained minimally at 21-24%. (1, 3, 4, 6, 8) These recommendations are consistent with a recent survey of obstetricians and practice guidelines from the American Society of Anesthesiologists. (11) Ideally, the use of a single unit of PRBCs should increase the hematocrit by approximately 3-4% in a 70 kg patient. (12) However, the expected increase in hematocrit may be slightly less due to expanded blood volume during pregnancy. As noted elsewhere in this toolkit, any patient with continued bleeding after initial measures have failed (Stage 2) should have two units of PRBCs released from the blood bank. If these are not readily available, consideration should be given for the use of uncross-matched O negative blood while the blood bank is completing the patient’s type and crossmatch. Consistent with recommendations from this toolkit, for any patient that reaches Stage 3, a massive OB hemorrhage pack should be prepared, which includes an additional 4 or 6 units of PRBCs as pre-arranged with the blood bank for massive transfusion protocol. Good communication with the laboratory regarding the urgency of the situation is essential.

FRESH FROZEN PLASMA (FFP)
Fresh frozen plasma contains nearly all coagulation factors and can be used up to 24 hours after thawing and up to 5 days if relabeled as “thawed plasma.” Concomitant use of FFP and PRBCs is recommended during massive hemorrhage. Using a high ratio of PRBCs to FFP (1.5:1 or 1:1) has been shown to significantly improve survival from hemorrhage after trauma. (13) Similar recommendations have been established at centers with existing massive OB hemorrhage protocols with the goal of maintaining the INR at <1.5-1.7. (1, 3, 8, 14) (15) If diffuse bleeding is noted, or there is laboratory evidence of DIC and the patient has not been crossmatched, initial requests for 4 units of AB-FFP are recommended. AB plasma is usually in short supply and reserved for infants. However, 2-3 units of mismatched plasma can be transfused to adults while type and crossing is completed. FFP usually requires 30 minutes to thaw and will not be available immediately. Pre-arrangement with the blood bank for an inventory of thawed plasma for immediate issue may be considered if plasma usage volume is sufficient. If the patient enters into Stage 3 status, there should be no delays in preparation of FFP while waiting for laboratory results.

PLATELETS
All protocols in our review recommended transfusion of a single donor apheresis unit when platelet levels varied between 50,000-100,000 u/L. (3, 5, 7, 8) Platelet pheresis units are the standard equivalent of 6 units whole blood-derived pooled platelets and may increase the platelet count in a 70 kg patient by approximately 40-50,000/uL. (12) In the face of massive maternal hemorrhage, platelet transfusions should maintain platelet count between 50,000-100,000/uL. However, platelet counts should be used only as a guide and should be interpreted in conjunction with the patient’s clinical condition. These recommendations are consistent with those of the American Society of Anesthesiologists Task Force on Perioperative Blood Loss. (16) Some protocols have suggested higher platelet counts for initiating transfusion and maintaining
appropriate platelet levels. These suggestions are based on the assumption that unless bleeding and DIC have been controlled, the patient will experience ongoing platelet loss. (2, 3) Platelets do not require crossmatching and are generally not type specific. Rh negative platelets are given to patients with an Rh negative blood type because of the slight risk of sensitization to the D-antigen. However, a dose of Rh-Immune Globulin can be given and is protective if Rh negative platelets are unavailable.

**CRYOPRECIPITATE AND FIBRINOGEN**

In the face of hypofibrinoginemia (fibrinogen levels <100-125 mg/dL and ongoing bleeding), fibrinogen should be used in addition to FFP. Transfusion recommendations were based on maintaining a fibrinogen concentration above 100 mg/dL. Cryoprecipitate release from the Blood Bank is usually in groups of 6-10 units. Each unit provides $150 \text{ mg of fibrinogen for a total of at least } 1500 \text{ mg in a pool of 10 units}$ in a total volume of approximately 80-100 cc. A pooled “ten-unit” pack would be expected to increase the fibrinogen level of a 70 kg patient by approximately 75mg/dL. It is worth noting that a 10-unit pool represents 10 separate donor exposures. If continued bleeding and hypofibrinoginemia is present, additional units of cryoprecipitate should be used.

**RECOMBINANT FACTOR VIIA**

Factor VII is a vitamin K-dependent serine protease with a pivotal role in coagulation. After reconstitution with sterile water, each vial contains approximately 0.6 mg/mL (600 $\mu$g/mL). It is marketed for use in patients with hemophilia A and B. The role of rVII in primary postpartum hemorrhage is controversial. (17, 18) It has been reported to significantly improve hemostasis in hemorrhaging obstetrical patients, but may also result in life-threatening thrombosis. (19) When available, its use should be reserved for rescue therapy when conventional therapy has failed (i.e., after 10-12 units of PRBC, 6-10 units of FFP and 2-3 units of platelets). Dosing recommendations in obstetrical hemorrhage patients has not been uniform. See Appendix A for additional information.

**SUMMARY**

During obstetrical hemorrhage, the primary goals are to provide adequate blood product replacement and to either prevent or correct DIC. The literature and protocols reviewed provided remarkable consensus related to therapy in the setting of massive obstetrical hemorrhage.

**RECOMMENDATIONS**

For transfusion in the setting of massive obstetrical hemorrhage, use a ratio of PRBCs to FFP to platelets that is 6 units PRBC: 4 units FFP: 1 unit pheresis platelets. If bleeding continues after initial treatment, strong consideration should be given to increasing the amount of FFP to a ratio of 4 units PRBC: 4 units of FFP: 1 unit of pheresis platelets.
STAT LABS
If bleeding exceeds expected volume for routine delivery and there is no response to initial therapy, request stat laboratory analysis for the following:
   1) CBC with platelets
   2) PT/PTT
   3) Fibrinogen
Repeat labs 1-3 every 30 minutes until patient is stable.
A glass red-top tube without additives should be collected and taped to the wall and checked after 10 minutes; if the red-top blood is not clotted at 10 minutes, assume patient has DIC until laboratory test(s) show otherwise. Note that per OSHA regulations, many hospitals are now using plastic red top tubes, which contain an additive to induce clotting; in glass tubes, clotting was induced by the negative surface charge of glass. This simple test is reliable with the use of glass tubes, but not with plastic.

PBRCs
   • Initial request: 4-6 units of RBCs
   • O-negative or type-specific blood initially until cross match units are released

FFP
   • RBCs to FFP ratio not to exceed 3:2
   • Infuse FFP to maintain INR <1.5

PLATELETS
   • Single donor apheresis platelet pack
   • Infuse to maintain platelet count >50,000-100,000/uL in the face of ongoing hemorrhage

CRYOPRECIPITATE
   • Initial request: 10 units cryoprecipitate if fibrinogen is less than 100mg/dL
   • Additional units to maintain fibrinogen concentration ≥100-125mg/dL

RECOMBINANT ACTIVATED FACTOR VII (rVII)
If available, use when there is continued hemorrhage AND all other blood replacement therapies have failed (i.e., after the use of 10-12 units PRBC, 6-12 units FFP and 2-3 units platelets).

EDUCATIONAL TOOLS, SUPPORT DOCUMENTS
APPENDIX A: Use of Factor VIIA
APPENDIX B: Adverse Reactions to Transfusions

EVIDENCE GRADING
Level of Evidence: II-3C: Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. Strong quality improvement data, such as statistical process control or other well-designed analysis.
BLOOD PRODUCT REPLACEMENT: OBSTETRIC HEMORRHAGE
APPENDIX A: USE OF FACTOR VIIa

The use of Recombinant factor VIIa has been shown in a number of case series to reduce ongoing massive obstetrical hemorrhage. (19-22) The use of recombinant factor VIIa for obstetrical or trauma hemorrhage would be considered “off label” use. Dosing for recombinant factor VIIa in trauma and obstetrical patients has varied (60-90 mcg/kg) and no studies have attempted to identify the ideal dose in the setting of maternal hemorrhage. (21) Anecdotal experience from members of this committee suggests that lower dosages have also been effective. It should be noted that most members of this committee who have experience using recombinant VIIa have reported anecdotal cases of maternal thrombosis; unfortunately, none of these have been reported in the literature.

The committee recognizes that recombinant factor VIIa may not be available in smaller centers and/or non-trauma centers. If available, its use should be limited to patients after reasonable attempts for correction of ongoing bleeding with conventional therapy have failed (i.e., after the use of 10-12 units PRBC, 6-9 units FFP, 2-3 apheresis platelet units and cryoprecipitate). In addition, prior to treatment the patient’s platelet count should be ≥50,000/uL. If the patient’s platelet count is not ≥50,000/uL, platelets should be given concurrently. Due to their negative impact on all coagulation factors, correction acidosis and/or hypothermia is essential for successful use of recombinant factor VIIa.

Based on available data, initial dosing of recombinant factor VIIa should be between 30-90 mcg/kg and repeated in 20-30 minutes if <90 mcg/kg was used and there was no clinical response. Additional dosing may be helpful if there was no initial clinical response and if hypothermia and/or acidosis have been corrected. Adoption of a massive obstetrical hemorrhage policy that includes recombinant factor VIIa should be reviewed and approved in conjunction with laboratory medicine, pharmacy and the local blood bank depending on who supplies and distributes this agent. If there is continued coagulopathy, and an initial response was seen, additional dosing may be used in 2-3 hours due to the relatively short half-life of recombinant factor VIIa. Further treatment should be provided in consultation with a local and/or regional expert in the area of maternal coagulopathy/massive obstetrical hemorrhage. It should also be emphasized that the use of conventional therapy (PRBCs, platelets, FFP, and cryoprecipitate) should also continue.
## Acute Adverse Effects of Transfusion
(Onset within minutes or hours)

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Incidence</th>
<th>Usual Cause</th>
<th>Signs or Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis-Immunologic (Acute Hemolytic transfusion reaction)</td>
<td>1:25,000</td>
<td>Red cell incompatibility, usually ABO</td>
<td>Fever, chills, renal failure, DIC, pain, hypotension, tachycardia, anxiety, hemoglobinemia, hemoglobinuria, cardiac arrest.</td>
</tr>
<tr>
<td>Hemolysis-Physical or Chemical</td>
<td>Unknown</td>
<td>Overheating, freezing, addition of hemolytic drugs or solutions.</td>
<td>Asymptomatic hemoglobinuria, rarely DIC, renal failure, hypotension</td>
</tr>
<tr>
<td>Febrile Nonhemolytic</td>
<td>0.5-1.5%</td>
<td>Recipient antibodies to donor leukocytes; or preformed cytokines in blood product</td>
<td>Fever, chills</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1:20,000-47,000</td>
<td>IGA deficient recipient with antibodies to IgA in donor plasma; antibodies to other plasma proteins, WBCs and platelets.</td>
<td>Respiratory obstruction and cardiovascular collapse, angioedema, anxiety, chills, agitation.</td>
</tr>
<tr>
<td>Urticarial</td>
<td>1-3%</td>
<td>Antibody to donor plasma proteins</td>
<td>Pruritis and hives</td>
</tr>
<tr>
<td>Transfusion Related Acute Lung Injury (TRALI, Non-cardiogenic Pulmonary Edema)</td>
<td>Reported 0.001%, 0.02%, 0.34%</td>
<td>DONOR antibody to recipient leukocytes or patient antibody to donor specific HLA or granulocytes</td>
<td>Respiratory distress, pulmonary edema and hypoxemia with normal wedge pressures. “White out” on CXR</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Unknown</td>
<td>Volume overload</td>
<td>Respiratory distress</td>
</tr>
<tr>
<td>Septic Complication</td>
<td>1:1000-7:1000</td>
<td>Bacterial contamination</td>
<td>Usually gram negative sepsis when the transfusion is red cells, gram positive cocci are most common in platelet transfusion</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Unknown</td>
<td>Rapid infusion of cold blood</td>
<td>Chills without fever</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Unknown</td>
<td>RAPID infusion of stored red cell</td>
<td>Cardiac dysfunction (usually problematic only in infants or those with compromised renal function)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Unknown</td>
<td>RAPID AND MASSIVE transfusion of stored blood Prophylactic administration of Calcium is not recommended.</td>
<td>Cardiac dysfunction (usually problematic only in patients with SEVERE hepatic insufficiency or neonatal massive exchange transfusion)</td>
</tr>
</tbody>
</table>
### Delayed Adverse Effects of Transfusion
(Onset within days to years)

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Incidence</th>
<th>Usual Cause</th>
<th>Signs or Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMUNOLOGIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Hemolytic Transfusion Reaction</td>
<td>1:4000-7000</td>
<td>Alloantibody to RBC antigen, usually anamnestic</td>
<td>Fever, chills, jaundice, pain, uncommonly renal failure days to weeks following transfusion</td>
</tr>
<tr>
<td>Graft vs Host Disease</td>
<td>Unknown but rare</td>
<td>Lymphocytes from blood donor mount an immune response to host antigens, usually in an immunocompromised host</td>
<td>Fever, rash, anorexia, diarrhea, -LFTs, <strong>PROFOUND PANCYTOPENIA</strong> which leads to death</td>
</tr>
<tr>
<td>Post-transfusion Purpura</td>
<td>Rare</td>
<td>Alloantibody to platelet antigen (usually anti-HPA-1a)</td>
<td>Thrombocytopenia and generalized purpura</td>
</tr>
<tr>
<td>Red Cell Alloimmunization</td>
<td>≈2% of transfused patients</td>
<td>Exposure to foreign red cell antigens</td>
<td>May cause delayed hemolytic reactions on subsequent transfusions</td>
</tr>
<tr>
<td>Platelet-re refractoriness</td>
<td>≈30% of patients requiring multiple plt txs</td>
<td>Exposure to foreign HLA antigens, sepsis, depressed hematopoiesis, splenic sequestration.</td>
<td>Poor response to platelet transfusions</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>Unknown</td>
<td>Leukocytes in transfused products</td>
<td>May increase risk of infection or tumor recurrence.</td>
</tr>
<tr>
<td><strong>NONIMMUNOLOGIC</strong></td>
<td></td>
<td></td>
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<tr>
<td>Iron Overload</td>
<td>Dependent on number of red cell transfusion</td>
<td>Iron in transfused red cells, usually need 60+ units in an adult patient</td>
<td>Hemochromatosis, cardiac dysfunction</td>
</tr>
</tbody>
</table>
## Delayed Adverse Effects of Transfusion
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<tr>
<td><strong>INFECTIOUS</strong></td>
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<tr>
<td>HIV</td>
<td>1:2,135,000</td>
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<td></td>
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<tr>
<td>Hepatitis B</td>
<td>1:205,000</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C</td>
<td>1:1,935,000</td>
<td></td>
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<tr>
<td>HTLV I/II</td>
<td>1:2,993,000</td>
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<tr>
<td>CMV</td>
<td>&lt; 1% of seropositive units transmit disease</td>
<td></td>
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<tr>
<td>Protozoal infections (Malaria, Babesia, Chagas disease)</td>
<td>Rare</td>
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<tr>
<td>Parvovirus B19</td>
<td>40-60% of donors are seropositive but viremia occurs only during acute phase of infection</td>
<td>A non-enveloped ssDNA virus which is not inactivated by solvent-detergent methods of viral inactivation. Has been detected in pooled factor concentrate products</td>
<td>Intrauterine infection: may lead to hydrops fetalis and fetal demise, children: Fifth's disease, Pt's with chronic hemolytic syndromes or Immune deficiency: aplastic crisis</td>
</tr>
<tr>
<td><strong>Potential or Theoretical Risks</strong></td>
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<tr>
<td>Creutzfeld-Jacob Disease (Theoretical risk)</td>
<td>Cases of transmission by transfusion products have never been reported or suspected. Injection of buffy coats from CJD pts directly into brains of lab animals has resulted in spongiform encephalopathy</td>
<td>Abnormal prion which behaves as an infectious particle</td>
<td>Progressive dementia resulting in death</td>
</tr>
<tr>
<td>As yet unknown infections (Potential risk)</td>
<td>Unknown</td>
<td>Infectious agents which may be detected in the future</td>
<td>Unknown morbidity and mortality</td>
</tr>
</tbody>
</table>
**IMMEDIATE STEPS FOR ALL REACTIONS:**

1. Stop transfusion.
2. Keep IV open with 0.9% NaCl.

**If transfusion is terminated:**

1. Send freshly collected blood and any necessary urine samples to Blood Bank.
2. Send blood unit and administration set to Blood Bank.
3. Fill out COMPLETELY and send to Blood Bank the Transfusion Reaction section of the blood tag.

**Source:** Harbor-UCLA Medical Center Appendix to Hospital Policy for Informed Consent for Blood and Blood Products, initially developed by Priscilla Figueroa, MD 8/1998 and most recently revised by Holli M. Mason, MD 1/2010; based on information from the American Association of Blood Banks

**REFERENCES**