Lesson S43: Management of the Patient Requiring Blood Transfusion

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Professional Gaps

Blood transfusions carry the risk of complications, both major and minor. However, in many situations, replacement of blood or blood products may be lifesaving. The American Society of Anesthesiologists presented updated guidelines on the use of blood products to help the practitioner develop perioperative plans to decrease the need for transfused products and to better understand the risks. These new guidelines are based on an extensive review of the literature as well as consultant and practitioner experience and will likely be illuminating for most anesthesiologists.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. State the incidence of antibodies found on routine cross matching
2. Cite the frequency of common complications of blood transfusion
3. Explain how blood is typed and cross matched
4. Discuss the incidence of blood product replacement
5. Formulate perioperative plans to decrease the need for blood transfusion
6. Identify the proper situation for tranexamic acid administration
7. Present a brief background of blood transfusion
8. Plan for perioperative preparation in an anemic patient
9. Describe the current protocol for testing donated blood
10. Distinguish between type and screen and type and cross match

Case

A 59 year old woman presented to the clinic for preanesthetic evaluation prior to undergoing a radical hysterectomy with extensive node resection for invasive cervical cancer. Apart from vaginal bleeding that had been ongoing for 2 months, she was otherwise relatively healthy and performed activities of
daily living without difficulty. She reported that the surgeon informed her that she would probably require blood transfusion and suggested that she pre-donate 2 units. She agreed with the surgeon as she had read on the internet that there was an increased risk of severe complications and even death from receiving a mismatched blood transfusion or blood that may be tainted with virus. Her hematocrit was 31%. She had given birth to 2 children and had no history of prior transfusion. She was unaware of her blood type or her children’s blood types. She reported no known allergies.

Introduction

Statistics from the U.S. Department of Health and Human Services (HHS) National Blood Collection and Utilization Survey Report (NBCUS) on the collection and transfusion of blood for 2011 show that more than 9 million blood donors in the United States supplied 14.5 million units, which represented a statistically significant decrease of 9.1% since 2008. Transfusion of white and red cells declined by 8.2% to 13.8 million units. A total of 20.9 million components were transfused, a decrease of 11.6%. With new national-level initiatives on blood safety, 30% of hospital respondents in 2011 noted that patient blood management is now a formal program in their facilities.

Transfusion related events occur in about 20% of transfusions, with serious adverse complications occurring in 0.1% of transfusions of red cell replacement and 0.04% of platelet infusions. Section 606.170(b) of Title 21, Code of Federal Regulations (21 CFR 606.170(b)), requires that facilities notify the Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), Office of Compliance and Biologics Quality (OCBQ), as soon as possible after confirming a fatality due to a complication of blood collection or transfusion. The collecting facility must report donor fatalities, and the compatibility testing facility must report recipient fatalities. The regulation also requires the reporting facility to submit a report of the investigation within 7 days of the fatality. According to the FDA, 54 deaths were reported in 2008, 66 deaths in 2009, 64 deaths in 2010 and 58 deaths in 2011. The FDA warns that these figures do not represent the true number because of inherent variation in reporting and accuracy. Also, these numbers do not include cases of deaths from disease transmission, patients who suffer a severe injury but survive, and others who have less serious but still disabling complications.

To provide proper perspective of the risk associated with transfusion, the American Society of Anesthesiologists (ASA) recently updated practice guidelines for perioperative blood management, emphasizing preoperative assessment, assessment of the risk of transfusion and the use of adjunct medications to prevent or treat bleeding.

Background

In the early history of blood transfusion - 18th and 19th centuries - transfusions were attempted from animals to humans resulting in catastrophic failures. The discovery of the ABO blood group antigens by Landsteiner in 1901 allowed some understanding of the immunological components of blood transfusion. More detailed blood cell typing evolved over the 20th century. The development of anticoagulant-preservative solutions permitted storage of blood.

Therapy using blood components, rather than whole blood, was made possible by the replacement of glass bottles with interconnected plastic containers in the 1960s. An automated blood cell separator was developed to collect different types of blood cells making the collection of platelets and stem cells for transplantation and cellular therapies possible. Around the same time, the risk of transmission of
blood-borne infectious agents, such as hepatitis, became apparent. In the 1970s a study of post-transfusion hepatitis was coordinated by one of the first biorepositories dedicated to blood safety and was funded by the National Institutes of Health (NIH). Soon after, a protein was discovered on the surface of red blood cells that allowed malarial parasites to infect the cells. This was the first demonstration of a specific function for a red cell surface antigen, and has become the foundation for malaria vaccine research.

In the 1980s, development of a screening test to detect human immunodeficiency virus (HIV) led to dramatic improvements in blood safety as well as understanding of HIV. The NIH funded the Retrovirus Epidemiology Donor Study (REDS) from 1989 to 2003 to determine the prevalence and incidence of HIV among blood donors and the risks of transmitting HIV and other viruses via transfusions. REDS-II is now underway to monitor newly discovered infectious agents in blood, determine the causes of transfusion reactions of unknown etiology, assess the effectiveness of new donor screening methods, and evaluate the donation process to improve the adequacy of the blood supply. Current protocols, in conjunction with the World Health Organization are:

1. evaluating the risks of transfusion-transmitted infectious agents;
2. comparing the incidence of transfusion-related acute lung injury (TRALI), a potentially life-threatening syndrome, in recipients who receive blood that contains human leukocyte antigen (HLA) antibodies with the incidence in recipients who receive blood without the antibodies;
3. exploring why some blood donors fail to provide an accurate or complete health history during initial screening; and
4. evaluating the correlation of donor iron and hemoglobin levels with the frequency of blood donation and the amount of blood donated.

Nucleic acid amplification testing (NAT) greatly improved detection of HIV in donated blood by reducing the window period for HIV from 3 weeks to 11 days and the window period for hepatitis C virus (HCV) from about 70 to 10 days. NAT was modified in 2003 to detect the West Nile virus (WNV). It is now used to screen all whole blood and plasma donations in the United States for HIV, HCV, and WNV. HIV and HCV infection associated with blood transfusion has been reduced to about 1 in 1.5-2.0 million blood units. Other transmitted diseases that are being investigated include Dengue virus, which infects 50-100 million people worldwide and causes more than 25,000 deaths annually, babesiosis (babesia microorganism are endemic in the northeast US), Chagas disease and Creutzfeldt-Jacob disease. Platelet products are also tested for bacterial infections since there is a higher risk for contamination during storage at room temperature. Testing is also performed for cytomegalovirus (CMV) because of risk to certain immunocompromised recipients, such as those with organ transplant or HIV or pregnant mothers. However, not all blood is tested for CMV in the United States. Other than positivity for CMV, any products tested positive for infections are discarded.

No doubt in the future there will be blood substitutes. Newer tests will diagnose and exclude other diseases such as influenza pathogen reduction technologies. Typing will depend more on DNA technology and increased understanding of stem cell biology will speed new transfusion therapies.

**Blood Typing**

Blood types are classified according to inherited antigenic substances on the surface of red blood cells (RBCs). These antigens may be proteins, carbohydrates, glycoproteins, or glycolipids, depending on the blood group system. A total of 30 human blood group systems are now recognized by the International
Society of Blood Transfusion (ISBT). The same blood group generally remains for life but very rarely may be changed through addition or suppression of an antigen in infection, malignancy, or autoimmune disease or after bone marrow transplantation.4,5

The Rh system is the second most significant blood-group system with about 50 antigens. The most important of the five dominant Rh antigens is the D antigen, because it is most likely to provoke an immune system response. It is common for D-negative individuals not to have any anti-D IgG or IgM antibodies, because anti-D antibodies are not usually produced by sensitization against environmental substances. However, D-negative individuals can produce IgG anti-D antibodies following a sensitizing event such as a feto-maternal transfusion of blood during pregnancy or a blood transfusion with D positive RBCs.

**Antibodies**

The ABO system is the most important blood-group system in transfusion. The associated anti-A and anti-B antibodies are immunoglobulin M (IgM) antibodies. The terms antibody and immunoglobulin are often used interchangeably. ABO IgM antibodies are produced in the first years of life by sensitization to environmental substances such as food, bacteria, and viruses or during gestation.

**Typing and screening or cross matching**

The requisition slip for each specimen is carefully checked. Because of the risk of transfusion-related complications, the blood bank may reject a blood sample for even the smallest discrepancy, a requirement necessary to comply with the rules of the American Association of Blood Banks (AABB), national regulations and local policies.

The type determines the ABO-Rh status of the patient. The test requires approximately 15 minutes of incubating the recipient’s red cells with commercial anti-A and anti-B antibodies to determine if the patient has A or B antigens on the surface of the red cells. Incubation with commercial anti-D antibodies determines RhD status. While there are approximately 50 Rh antigens, the D antigen is considered the most immunogenic and is the only Rh antigen routinely tested. A second part of the type called “reverse” typing requires commercially available A and B reagent cells to test if the donor’s serum has naturally preformed antibodies to these antigens.

The screen is performed to detect non-A and non-B antibodies, and takes at least 30 minutes. There are approximately 30 discrete blood group systems that are currently identified, including ABO and Rh, encompassing over 250 antigens that coat the red cell surface. Approximately 18 antigens, those deemed most clinically significant, are required by the FDA to be present on reagent red cells used in the antibody screen. About 3-10% of persons who have had multiple blood transfusions have antibodies to these “unexpected” antigens.

The antibody screen reduces significantly the chance of incompatibility due to alloantibodies. The probability of this screening test missing an antibody that is potentially dangerous in the general population has been estimated to be no more than 1 in 10,000.6 In a recent review of 22,463 cases, positive results for antibody screening were found in 243 patients or 1.52%.7 Lewis, Rh, Xga and mixed antibodies were identified in 123 patients. For the remaining cases, the specifics of the antibodies could not be determined but 52% had a history of pregnancy and 20% had been transfused previously.
Screening is done by incubating the recipient’s serum with commercially available type O reagent cells that include the most clinically significant antibodies causing hemolytic transfusion reactions – approximately 18 of them. Agglutination or hemolysis of reagent cells indicates the presence of unexpected antibodies. Donors that do not express any of these antigens are located. This latter portion is called the cross match.

For a patient without a significant transfusion history, ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion, an antibody screen increases this chance to 99.94%, and a serologic cross match increases that number further to 99.95%.

**Types of Transfusion Reactions**

Reactions can generally be grouped as immunological or infectious. Complications can potentially arise directly or indirectly from quality degradation during storage. Some studies suggest that the way donated blood is processed and the amount of time it is stored may contribute to the development of non-infectious complications (red cells are stored for up to 6 weeks). The NIH is funding nine research projects to determine if the safety and efficacy of red blood cell transfusions vary depending on how long the cells have been stored.4,5

Overall, adverse events from transfusions in the US cost about 17 billion healthcare dollars – and, in effect, add more to the cost of each transfusion than acquisition and procedure costs combined.8 While some risks are inherent to the patient, all patients have a baseline risk of complications that increases in direct proportion to the frequency and volume of transfusion.

Several countries have transfusion surveillance systems in place. Overall, transfusion carries an incidence of severe reactions determined to be about 0.61% per unit.9,10,11 Mild symptoms such as fever and chills usually go unreported.

Some of the reactions are described in Table 1.

**Table 1. Adverse events resulting from transfusion of blood products**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>OCCURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute hemolytic reaction</strong></td>
<td>Occurs in about 0.016 percent of transfusions, with about 0.003 percent being fatal. Donor erythrocytes are destroyed by preformed recipient antibodies usually due to clerical errors or improper typing and cross matching. Symptoms include fever, chills, chest pain, back pain, hemorrhage, tachycardia, dyspnea, and hypotension. Treatment is supportive. Kidney injury may occur due to the effects of the hemolytic reaction.</td>
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<tr>
<td><strong>Delayed hemolytic reaction</strong></td>
<td>Occurs in about 0.025 percent of transfusions and is due to the same mechanism. The consequences are generally mild. Evidence of hemolysis and lowered hemoglobin levels may still occur. Treatment is generally not needed, but due to the presence of recipient antibodies, future compatibility may be altered.</td>
</tr>
<tr>
<td>EVENT</td>
<td>OCCURRENCE</td>
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<tr>
<td><strong>Febrile non-hemolytic reaction</strong></td>
<td>Due to the presence of recipient antibodies to donor white blood cells. Occurs in about 7% of transfusions and often related to prior transfusion exposure.</td>
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<tr>
<td><strong>Allergic reaction</strong></td>
<td>Occurs when the recipient has antibodies to certain chemicals in the donor blood. Symptoms include urticaria, pruritus, and may rarely result in anaphylactic shock.</td>
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<tr>
<td><strong>Post-transfusion purpura</strong></td>
<td>A rare complication that occurs after transfusion containing platelets that express a surface protein HPA-1a. Treatment is with intravenous immunoglobulin, and recipients should only receive future transfusions with washed cells or HPA-1a negative cells.</td>
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<tr>
<td><strong>Transfusion-associated acute lung injury (TRALI)</strong></td>
<td>An increasingly recognized adverse reaction.(^{12,13}) It is a syndrome of acute hypoxia occurring within 6 hours of transfusion. It may occur as often as 1 in 5000 transfusions. TRALI is the leading cause (around 50% of cases) of transfusion-related fatalities in the United States.(^{17}) The complication is typically associated with plasma products but can also occur in recipients of packed red blood cells, presumably due to the residual plasma present in the unit. Plasma infusions should be from male donors.</td>
</tr>
<tr>
<td><strong>Transfusion-transmitted bacterial infection</strong></td>
<td>Estimated at about 1 in 50,000 platelet transfusions, and 1 in 500,000 red blood cell transfusions.</td>
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<td><strong>HIV contamination</strong></td>
<td>Rare and estimated at about 1 in 3 million units.</td>
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<td><strong>Hepatitis C</strong></td>
<td>Risk is about 1 in 2 million units.</td>
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<tr>
<td><strong>Other transmissible infections</strong></td>
<td>Very rare and includes hepatitis B, syphilis, Chagas disease, cytomegalovirus infections (in immunocompromised recipients), HTLV, and Babesia.</td>
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<tr>
<td><strong>Transfusion-associated volume overload</strong></td>
<td>Occurs mainly in recipients with underlying cardiac or kidney disease. Plasma transfusion is especially prone to causing volume overload due to its hypertonicity.</td>
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<tr>
<td><strong>Hypothermia</strong></td>
<td>Occurs typically with transfusions of large quantities of blood products.</td>
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<tr>
<td><strong>Coagulopathies</strong></td>
<td>Includes disseminated intravascular coagulation, dilution of recipient platelets and coagulation factors, hypothermia and can occur with large volume transfusions.</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td>Occurs as a result of the breakdown of citrate stored in blood into bicarbonate.</td>
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Practice Guidelines

The recent guidelines from the ASA derive evidence from 277 references as well as consultant and practitioner opinions, forums and clinical feasibility data. They differ from earlier ones in that a greater emphasis is placed on perioperative patient assessment. The following is a synopsis of several of the important recommendations.

**Patient Evaluation**

- Review medical records, and interview patient and family to determine history of previous transfusions, drug induced coagulopathy (including herbals), congenital coagulopathy, thrombotic events, and risk factors for organ ischemia that may affect the transfusion trigger
- Inform the patient of the potential risks and benefits of transfusion
- Review pertinent laboratory test results
- Order additional tests as indicated (e.g., for coagulopathy)
- Conduct a physical examination for ecchymosis, petechiae, etc.
- If possible, conduct the preanesthetic evaluation well in advance to allow proper preparation

**Pre-admission Patient Preparation**

- Erythropoeitin, with or without iron, may be given to reduce the need for allogenic blood in selected patients (e.g., renal insufficiency, chronic anemia, refusal of transfusion)
- Iron for iron deficiency anemia, if time permits
- Discontinue anticoagulants after appropriate consultation and/or transition to a shorter acting agent for elective surgery. Aspirin may be continued on a case by case basis.
- Consider and be aware of the risk of thrombosis versus increased bleeding when the coagulation status is altered
- Assure the availability of blood and blood components
- Advise pre-donation only when there is time for erythropoietic reconstitution

**Pre-procedure Preparation**

- Use of multimodal protocols or algorithms to reduce usage
- Restrictive blood transfusion strategy; tolerance of a lower Hb/Hct on a case-by-case basis
- Administer blood, unit by unit with interval reevaluation
- Use of a massive transfusion protocol to optimize delivery in massively bleeding patients
- Use of a maximal surgical blood order schedule in accordance with institutional policies
- Reversal of anticoagulants: urgent reversal of warfarin and use prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP); non-urgent and use vitamin K unless rapid anticoagulation is required post-surgery
- Use anti-fibrinolytics for prophylaxis of allogenic blood use in cardiopulmonary bypass, liver surgery and orthopedic surgery
- Consider acute normovolemic hemodilution in patients at high risk for excessive bleeding
Intra- and post-operative management

- Administer allogenic blood without consideration of duration of storage
- Leukocyte-reduced blood may reduce complications of allogenic transfusion
- Reinfuse recovered red cells as a blood sparing intervention
- Periodically conduct a visual assessment with the surgeon to assess coagulopathy versus surgical bleeding
- Apply quantitative measurements of blood loss
- Monitor vital organ perfusion; standard ASA monitors and additional monitoring
- Monitor Hb/Hct if anemia is suspected
- Coagulation tests for suspected coagulopathy (INR, aPTT, fibrinogen, TEG, ROTEM)
- Periodically check for a transfusion reaction; if necessary, stop the transfusion and notify the blood bank

Treatment of excessive bleeding

- Platelet count before transfusion of platelets; give if count <50x10^9/l
- Coagulation tests before administering FFP. Give if INR >2 in the absence of heparin, transfused > 1 blood volume or PT, aPTT 1.5X normal.
- Assess fibrinogen levels before cryoprecipitate and give if fibrinogen < 80-100mg.dl with excessive bleeding.
- Desmopressin for excessive bleeding and platelet dysfunction, and also Von Willebrand’s disease
- Topical hemostatics like fibrin or thrombin glue
- Antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid if fibrinolysis is documented
- PCCs for excessive bleeding and increased INR
- Recombinant activated factor VII when no other alternative
- Fibrinogen concentrates

Management of the Case

The patient was found to have blood type O+ without any detectable antibodies. With 2 weeks remaining before the planned surgery, she was started on iron and erythropoietin. Pre-donation was not advised. Family donor directed blood was not an option as both her children lived in other countries and she was a widow. She was normotensive and was told that her blood pressure would be maintained at slightly lower levels while her cerebral function would be monitored with cerebral oximetry. A cell saver was made available and 2 units of blood typed and cross matched. She was assured that the risk of disease transmission was very low and after given her medical history, the chance of other reactions also negligible.

She was anesthetized with a balanced technique including sevoflurane and fentanyl. Mean blood pressure was maintained at 80mmHg. A total of 525ml of blood from the cell saver was returned, starting 2 hours after incision. A one unit allogenic transfusion was required. Surgery lasted for almost 5 hours. Blood loss was estimated at 2l. The final Hct was 29%. She awoke promptly. On the 2nd post-operative day, her hematocrit was found to be 26% but it was deemed she did not require further transfusion and she was discharged home 3 days later on an iron regimen.
Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanaesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).

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5. NIH Clinical Center Contact: Clinical Center Communication. http://clinicalcenter.nih.gov


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**Post-test**

1. **Statistics from HHS show that the number of blood component units transfused in the United States is estimated to be:**
   a. Increasing at an alarming rate  
   b. About 20 million  
   c. Close to 100 million  
   d. Largely unknown

2. **Adverse events related to transfusion of red cells and platelets are estimated to be:**
   a. 0.1% and 10%  
   b. 5% and 0.04%  
   c. Variable, depending on the sex of the donor  
   d. 0.1% and 0.04%

3. **A FALSE statement regarding TRALI:**
   a. It is the leading cause of transfusion related fatalities  
   b. It is usually associated with plasma transfusions  
   c. It typically occurs 72 hours post-transfusion of platelets  
   d. The incidence can be reduced by using only male donors

4. **With no significant transfusion history:**
   a. ABO-Rh typing allows a compatibility transfusion of 99.8%  
   b. Addition of an antibody screen increases the safety to 99.94%  
   c. Serologic cross matching adds an additional 0.01% safety  
   d. All of the above

5. **During serologic cross matching:**
   a. Donor plasma and recipient red cells are incubated  
   b. Donor red cells and recipient plasma are examined for agglutination  
   c. A temperature of 35 degrees is required  
   d. No longer than 10 minutes are necessary to get accurate results
6. Complications of blood transfusions are due to:
   a. Immunologic compromise
   b. Infectious contamination
   c. Degradation during storage
   d. All of the above

7. A correct statement regarding the antibody screen:
   a. The process takes at least 60 minutes
   b. Testing for 18 clinically significant antigens is required
   c. Testing for all 250 antigens that coat the red cell surface is required
   d. About 30% of persons who received prior transfusions have antibodies to unexpected antigens

8. Acute hemolytic reaction and delayed hemolytic reaction are the same in that both adverse reactions:
   a. Are caused by destruction of donor erythrocytes by preformed recipient antibodies
   b. Can be fatal
   c. Require aggressive treatment
   d. Have non-specific mild symptoms

9. Pre-admission patient preparation for a patient with chronic anemia can include:
   a. Erythropoetin
   b. Transfusion prior to procedure
   c. Pre-donation
   d. None of the above are options

10. Recommendations for treatment of excessive bleeding include:
    a. FFP if INR > 2 in the absence of heparin
    b. Desmopressin
    c. Fibrinogen concentrates
    d. All of the above