Blood Transfusions: An Overview

Jassin M. Jouria, MD

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Abstract

Being able to replace blood and blood components that a patient has lost or that his or her body is not able to produce is a vital part of providing excellent medical care. With the aid of donor blood, or even sometimes the patient’s own blood that has been previously banked, medical professionals have a safe strategy for treatment of patients who have lost blood to illness or injury. This course will explain the different types of blood products, the requirements for performing a transfusion, and how to recognize and respond to complications of the transfusion process.
Continuing Nursing Education Course Director & Planners

William A. Cook, PhD, Director, Douglas Lawrence, MA, Webmaster,
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Statement of Need

The transfusion of blood and blood products provide life-saving measures and treat various medical conditions. Nurses are required to follow blood transfusion guidelines and protocol to ensure patient safety and wellbeing.

Course Purpose

To provide nursing professionals with knowledge of blood and blood product
indications and administration protocol for safe administration.

**Learning Objectives**

1. Explain the difference between whole blood and blood components.
2. Describe circumstances that require fresh frozen plasma.
3. Identify the requirements for giving a blood transfusion.
4. Explain the documentation requirements for transfusions.
5. List common causes of transfusion reactions.
7. Describe the process to treat a patient with a reaction to a transfusion.

**Target Audience**

Advanced Practice Registered Nurses, Registered Nurses, Licensed Practical Nurses, and Associates

**Course Author & Director Disclosures**

Jassin M. Jouria, MD, William S. Cook, PhD, Douglas Lawrence, MA, Susan DePasquale, CGRN, MSN, FPMHNP-BC – all have no disclosures

**Acknowledgement of Commercial Support**

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**Activity Review Information**

Reviewed by Susan DePasquale, CGRN, MSN, FPMHNP-BC

**Release Date:** 5/14/2015  
**Termination Date:** 5/14/2018
1. GM is a 32-year-old AA female who is typed with B+ blood. As a donor, GM can MOST SAFELY provide packed RBC for which of the following individuals?
   a. TS, a 21 year old Asian female with AB+ blood
   b. KT, a 56 year old European male with AB - blood
   c. PL, a 76 year old white female with A - blood
   d. MN, a 5-year-old Hispanic male with B+ blood

2. Your patient is an otherwise healthy 46-year-old male with β-thalassemia and is scheduled for a transfusion of packed RBC. You are with him and are explaining some of the risks and benefits of his upcoming transfusion. Which of the following would be true?
   a. He runs a high risk of graft-versus-host disease along with allergic reactions, a fever, a hemolytic reaction and some very rare reactions but that he will be observed and monitored throughout the transfusion.
   b. He runs a high risk of Transfusion-Related Acute Lung Injury (TRALI) or Transfusion Associated Circulatory Overload (TACO) but that he will be observed and monitored throughout the transfusion.
   c. You should counsel him not to get a transfusion, but to get a shot of iron for his iron deficiency anemia.
   d. The transfusion should be completed within 4 hours and there are some risks associated with an RBC transfusion, including
allergic reactions, a fever, a hemolytic reaction and some very rare reactions but that he will be observed and monitored throughout the transfusion.

3. Your patient is typed AB— and is scheduled for an infusion of plasma. Which of the following plasma types is most suitable for your patient?
   a. AB+
   b. O-
   c. A+
   d. B-

4. A patient who is thrombocytopenic is scheduled to receive two units of irradiated platelets from which the leukocytes (WBC) have been removed. You spike the unit with a standard infusion set and get ready to connect directly to her right arm. Something makes you stop—what question do you need to ask yourself?
   a. Don’t I need to use a standard blood filter?
   b. Shouldn’t I use another leukocyte reduction filter just to be sure her chances of GVHD are reduced?
   c. I should probably ask the blood bank if these platelets have been tested for ABO compatibility, shouldn’t I?
   d. I wonder if her platelet level is low enough to get two units of platelets?

5. Which of the following statements is FALSE?
   a. All blood components must be infused through a filter.
   b. The first 15 minutes of a transfusion should be at a slow rate to ensure there are no acute reactions to the transfusion
c. Nurses can store blood products in the medication refrigerator as long as the temperature is monitored.
d. If a patient has a history of cold agglutinins, a blood-warming unit may be ordered, but it is not absolutely required.

6. A transfusion is started at 9:30 am. The packed RBCs were signed out of the blood bank at 8:30 am, but the patient’s IV has blown. It is now 10:30 am and the transfusion is not complete. At what time should the transfusion be stopped, whether or not it is complete?
   a. By 12:30 pm—4 hours after the blood was signed out.
   b. By the end of the shift—at 11 am
   c. By 4:30 pm - blood should be used within 8 hours of signing out of the blood bank.
   d. It doesn’t matter because the packed RBCs have been irradiated, so there is little risk of infection.

7. You notice that your patient’s temperature has gone up 0.5\degree in the last 15 minutes. She is receiving one unit of packed RBC, one unit of apheresis platelets and one unit of fresh frozen plasma. She is also complaining of cold and chills. What should you do?
   a. Give her a warming blanket
   b. Slow down the transfusion rate
   c. Stop the transfusion immediately
   d. Nothing—everything seems normal

8. Which of the following should NOT be infused in the same line with any blood component.
   a. 5% dextrose in water (D5W)
   b. 0.2% saline
c. Normal saline
d. Ringer’s solution

9. A first-time donor comes into the blood bank and has a few questions. She asks whether her blood will be tested for bacteria and viruses. Which of the following pathogens is not routinely tested for?
   a. Hepatitis
   b. Treponema
   c. Enterovirus B
   d. CMV

10. An acute hemolytic reaction during a transfusion for acute blood loss is most likely due to:
   a. ABO incompatibility
   b. Too rapid infusion
   c. Rh₀D incompatibility
   d. Massive sepsis
Introduction

According to a report from the Agency for Healthcare Research and Quality (AHRQ), blood transfusions were the most common hospital procedure in 2010, indicating that 11% of all hospital stays underwent at least one transfusion procedure.¹ This represented more than a 126% increase since 1997 and reached across all age groups, except for individuals less than one year old.

The American Association of Blood Banks (AABB) estimates that over 9.2 million volunteers donate blood and blood components every year. Approximately 30% of those are first time donors; together, all these donors represent about 15.7 million units of blood and blood components.² There is, however, significant variability in transfusion outcomes in a number of clinical settings. This variability may reflect deviations from practice guidelines, training differences, differences in recommendations of various medical societies, differences in availability of inventory and disagreements about the validity of the practice guidelines.³

While blood transfusions are generally accepted as being life-saving, this has actually not be tested in any prospective controlled trial.³ While the number of deaths associated with blood transfusions is small and seems to be decreasing,⁴ blood transfusions still carry

Normal RBCs with biconcave disc morphology
significant risk, are expensive, and face potential shortages in emergencies.

The American Association of Blood Banks (AABB) has initiated a Patient Blood Management (PBM) program with the goal of optimizing the care of transfusion patients and has produced guidelines for PBM and blood utilization. Blood management can be defined as a “patient-centered standard of care in which strategies and techniques are used to reduce, eliminate, or optimize blood transfusions to improve patient outcomes.” The guidelines include:6

- Development of guidelines specific to individual facilities and for quality improvement
- Providing thresholds and assessment strategies for the transfusion review process
- Both surgical and non-surgical strategies for PBM
- Procedures for auditing blood utilization

Successful PBM programs most often have a committed leader, and this is most often a registered nurse (RN) or an advanced practice registered nurse (APRN). The nursing staff often has the responsibility to implement the PBM programs, assess and manage transfusions and the potential reactions, as well as communicate to the patient and their family the benefits and potential adverse reactions to a blood transfusion. This activity is designed to review basic information about transfusions, provide information on potential complications and the current best practice guidelines, procedures and policies to manage complications and to inform health teams and patients regarding new developments in alternatives to allogeneic blood transfusions, including autologous transfusions, erythropoiesis-stimulating agents and hemostatic agents.7
Overview Of Transfusions Of Blood And Blood Components

Whole blood is rarely transfused anymore because of safety issues and practical concerns about the effective use of a unit of donated whole blood. It is much more efficient to use components rather than whole blood because more patients can benefit from this process. The different types of transfusions include:

- Packed red blood cells or packed RBCs (most often washed free of plasma)
- Plasma
- Clotting factors
- Platelets
- Intravenous Immunoglobulins or IVIG (i.e., RhoGam™)

Cellular therapies, often considered forms of transfusions and defined as using components derived from whole blood donations include hematopoietic stem cell transplants and bone marrow transplants.

Current Guidelines For Packed Red Blood Cell Transfusion

Recommendations for blood transfusion undergo constant debate and revision. The oldest (and often still repeated) rule quoted is the “10/30” rule, which states that the hemoglobin levels of surgical patients should be at or above 10g/dL and the hematocrit should be at or about 30%. However, this rule is not based on any direct evidence. Various professional organizations have developed their own criteria or guidelines for transfusions. There are many overlaps in these criteria. One of the broadest and all-encompassing

[10]
sets of guidelines is from the American Society of Hematology (ASH) and the American Association of Blood Banks (AABB) and are cited in this review. It should be remembered that the nursing staff must also bear in mind the policies and guidelines held to by their individual hospitals and institutions, and that it is the professional and ethical responsibility of the nursing staff to adhere to their institutional policies and guidelines. The ultimate clinically relevant verdict on safety and efficacy of transfusion should be based on effect on a patient's outcome, and whether transfusion improves it. For reference, a comparison of some of the clinical guidelines from other professional organizations is given in Table 1.

Table 1: Guideline Comparisons from individual professional organizations. Adapted from From the American Society of Hematology:8-12

<table>
<thead>
<tr>
<th>Target Population for guidelines</th>
<th>AABB</th>
<th>College of American Pathologists (CAP)</th>
<th>Society of Critical Care Medicine (SCCM)</th>
<th>Society of Thoracic Surgeons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin levels requiring RBC transfusions</strong></td>
<td>Hospitalized, hemodynamically stable</td>
<td>General</td>
<td>Critically Ill</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>Hb ≤7 g/dL in critically ill patients; Hb ≤8 g/dL in surgical patients or patients with pre-existing cardiovascular disease; When symptoms are present.</td>
<td>Based on clinical</td>
<td>Rarely for Hb &gt;10g/dL</td>
<td>Rarely for</td>
<td>Rarely for</td>
</tr>
<tr>
<td>Hb &lt;6 g/dL</td>
<td>Hb &lt;6 g/dL</td>
<td>Hb &lt;7 g/dL if ventilated, trauma, or stable cardiac disease (Hb &lt;8 g/dL in acute coronary syndrome)</td>
<td>Hb &lt;6 g/dL (Hb &lt;7 g/dL in postoperative patients and higher if risk of end-organ ischemia)</td>
<td></td>
</tr>
<tr>
<td>Decision: Patients with acute coronary syndrome</td>
<td>decisions: Hb 6-10g/dL</td>
<td>Hb&gt;10g/dL</td>
<td>Hb&gt;10g/dL</td>
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<tr>
<td>Hb levels as well as symptoms (chest pain, orthostatic hypotension, unresponsive tachycardia, heart failure)</td>
<td>Peripheral tissue oxygenation, clinical signs and symptoms, Hb, extent/rate of bleeding</td>
<td>Volume status, shock, duration/extent of anemia, cardiopulmonary parameters</td>
<td>Age, severity of illness, cardiac function, ischemia, extent/rate of blood loss, Hb, SVO₂</td>
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</table>

**Proper Uses Of Red Blood Cell (RBC) Transfusion**

- Treatment of symptomatic anemia
- Prophylaxis in life-threatening anemia
- Restoration of oxygen-carrying capacity in case of hemorrhage
- RBC are also indicated for exchange transfusion
  - Sickle cell disease
  - Severe parasitic infection (malaria, babesiosis)
  - Severe methemoglobinemia
  - Severe hyperbilirubinemia of newborn

RBC transfusion is not routinely indicated for *pharmacologically treatable anemia*, such as:

- Iron deficiency anemia
- Vitamin B12 or folate deficiency anemia

**Dosage and Administration**

- One unit of RBC will raise the hemoglobin of an average-size adult by ~1g/dL (or raise HCT ~3%)
- ABO group of RBC products must be compatible with ABO group of recipient
- RBC product must be serologically compatible with the recipient (see Pretransfusion Testing). Exceptions can be made in emergencies (see Emergency Release of Blood Products).
- Rate of transfusion
  - Transfuse slowly for first 15 minutes
    - Complete transfusion within 4 hours (per FDA)

**Special Processing Requirements of RBC for Transfusions**

There are times when special processing requirements exist for RBC transfusions. These are designed to minimize the risk of transfusion reactions in various ways. Leukocyte reduction, or the removal of white blood cells (WBC) from the donated blood minimizes the potential that a transfusion reaction based on the immune responses of those WBC can occur. These include reactions such as the febrile, non-hemolytic transfusion reactions. Leukocyte reduction can also minimize the risk that viruses, such as Cytomegalovirus (CMV) or herpes virus, are inadvertently transferred.\(^{13,14}\) However, leukocyte reduction does *not* prevent the possibility of Graft Versus Host Disease (GVHD); blood products and components must be irradiated in order to prevent GVHD.

Washing the blood cells removes plasma and removes pre-formed antibodies that may be present in the donor serum. This is particularly important to prevent the risk of anaphylaxis in IgA-deficient patient with anti-IgA antibodies.\(^{15,16}\) Washing the blood cells can also decrease the potential for reactions in patients sensitized by a history of previous transfusions.\(^{17}\)
Washing the cells must be performed under sterile conditions and using isotonic solutions to prevent contamination and hemolysis respectively.

Finally, blood and blood components may be irradiated to prevent graft-versus-host disease. This is most commonly done if the donor is a family member, from an HLA-selected donor or if the donor relationship to the recipient has not been established. It may also be done in preparation for an intrauterine transfusion and is commonly done for a number of pediatric conditions. Potassium (K⁺) levels may be elevated in these samples, though relatively rarely to clinically significant levels.¹⁸

Table 2: Pre-Treatments for Blood and Blood Components

<table>
<thead>
<tr>
<th>Process</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte Reduction</td>
<td>• Decrease risk of recurrent febrile, nonhemolytic transfusion reactions. • Decrease risk of cytomegalovirus (CMV) transmission (marrow transplant) • Decrease risk of HLA-alloimmunization <strong>Does not</strong> prevent transfusion associated graft-versus-host disease (TA-GVHD). To prevent TA-GVHD, irradiation is required.</td>
<td>• Most commonly achieved by filtration soon after collection • May be performed at bedside &lt;5x10⁶ leukocytes per product (per FDA)</td>
</tr>
<tr>
<td>Washing to remove residual plasma</td>
<td>• Decrease risk of anaphylaxis in IgA-deficient patient with anti-IgA antibodies • Decrease reactions in patients with history of recurrent, severe allergic or anaphylactoid reactions to blood product transfusion</td>
<td>• Isotonic saline must be used. Dextrose may be included. • Shelf-life of washed RBCs is 24 hrs at 1-6°C, but drops to 4 hrs at 20-24°C • Up to 20% of RBCs may be lost</td>
</tr>
<tr>
<td>Irradiation</td>
<td>• Prevention of TA-GVHD in certain circumstances: <strong>Donor categories</strong> • Product donated by family member • Product from HLA-selected donor</td>
<td>• Radiation dose: 2500 cGy (Gamma or X-irradiation) • Shelf life of irradiated product: up to 28 days unless original expiration date is sooner</td>
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<tr>
<td><strong>In pediatric practice</strong></td>
<td><strong>Products from directed donors whose relationship to recipient’s family has not been established</strong></td>
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<tr>
<td></td>
<td>Intrauterine transfusion (IUT)</td>
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<td></td>
<td>Exchange or simple transfusion in neonates if prior IUT</td>
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<tr>
<td></td>
<td>Congenital immune deficiency states</td>
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<tr>
<td></td>
<td>Acute leukemia: HLA-matched or family-donated products</td>
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<tr>
<td><strong>In adult or pediatric practice</strong></td>
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<tr>
<td></td>
<td>Allogeneic hemopoietic progenitor cell (HPC) transplant recipient</td>
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<td></td>
<td>Allogeneic HPC donor 7 days prior to, or during, HPC harvest</td>
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<td></td>
<td>Autologous HPC recipient</td>
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<tr>
<td></td>
<td>Hodgkin disease</td>
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<td></td>
<td>History of treatment with purine analogues and related drugs:</td>
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<tr>
<td></td>
<td>Fludarabine</td>
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<tr>
<td></td>
<td>2CDA (Cladribine®)</td>
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<td></td>
<td>Deoxycoformycin (Pentostatin®)</td>
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<td>Clofarabine (Clolar®)</td>
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<td></td>
<td>Bendamustine (Treanda®)</td>
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<td></td>
<td>Nelarabine (Arranon®)</td>
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<td></td>
<td>History of treatment with alemtuzumab (anti-CD52)</td>
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<tr>
<td></td>
<td>Aplastic anemia or rabbit antithymocyte globulin</td>
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**Note that K⁺ may be elevated.**

**When is Packed RBC Transfusion Required?**

In general, packed RBC transfusions are required for anemias of any etiology. It should be remembered that anemia is not a disease, but a
complex of signs and symptoms of cardiovascular and pulmonary compensatory mechanisms in response to some illness, condition or injury. Anemia, or the lack of sufficient red blood cells (RBC’s) to provide adequate oxygen to the tissues, can be caused by:

- **Deficiencies in erythropoiesis, or RBC production:**
  These can include iron deficiency anemia and anemias due to folate, vitamin B₁₂ and copper deficiencies. This type of anemia can also include aplastic anemia and the thalassemias.

- **Acute blood loss from injury or chronic blood loss from, for example, gastric or duodenal ulcers, coagulation disorders, gastritis, hypermenorrhea or hypothyroid disease.**

- **Excessive hemolysis due to:**
  Extrinsic defects or those not due to defects within the RBCs (these would include some autoimmune hemolysis, paroxysmal nocturnal hemoglobinuria, trauma and infections)

- **Intrinsic defects due to:**
  - Congenital RBC membrane defects such as hereditary elliptocytosis or acquired defects such as stomatocytosis or hypophosphatemia
  - Metabolic disorders such as hexose-monophosphate shunt defects (Glucose-6-phosphate deficiency [G6PD])
  - Hemoglobinopathies including sickle-cell anemia (SCA) and thalassemias (α, β, and β-δ)
When is an Other Blood Component Required?

Platelets

Platelets may be pooled from a number of donors or they may be derived from a single donor by platelet apheresis (see below). The platelets derived from a single donor in the apheresis donation have the advantage constitute a transfusion dose and are technically easier to pre-test (as opposed to the pooled platelets which must be tested at each donation, *i.e.*, 4-6 times). Another related advantage is that platelets form apheresis, and effectively reduce the potential for transfusion-transmitted infections and the incidence of allo-immunization by a larger number of platelet antigens from a pooled source. The platelet products should be leukoreduced (*i.e.*, have the WBCs removed) to reduce the likelihood of allo-immunization. The platelet products should also be irradiated to prevent graft-versus-host disease, which is nearly 100% fatal.

Platelet transfusion should not be based solely on the platelet count but should also be based on the presence, absence or likelihood of clinically relevant bleeding. Indications for platelet transfusion include the following conditions.

- **Prophylaxis for individuals with counts less than 20,000/μL (microliter):**
  - Acute leukemia (except for acute promyelocytic leukemia in unstable patients when the risk of alloimmunization is high)
  - Bone marrow aplasia
  - Myelodysplasias
- Autologous bone marrow transplants
- Autologous peripheral blood stem cell transplantation
- Bladder cancers or necrotic tumors
- Major surgery
- Bone marrow biopsy
- Other:
  - Lumbar puncture, epidural anesthesia, endoscopy with biopsy, placement of a central venous catheter, liver biopsy

- Chronically thrombocytopenic patients in whom bleeding is greater than the World Health Organization (WHO) grade 2:
  - World Health Organization has advised the following grading system:
    - Grade 0, none
    - Grade 1, petechiae, ecchymosis, occult blood in body secretions, and mild vaginal spotting
    - Grade 2, evidence of gross hemorrhage not requiring red cell transfusions over routine transfusion needs (i.e., epistaxis, hematuria, hematemeses)
    - Grade 3, hemorrhage requiring transfusion of 1 or more units of red cells per day
    - Grade 4, life-threatening hemorrhage, defined as massive bleeding causing hemodynamic compromise or bleeding into a vital organ (i.e., intracranial, pericardial, or pulmonary hemorrhage)

- Thrombocytopenia (platelets < 100,000/μL) due to reduced platelet production
• Active bleeding with thrombocytopenia (platelets < 100,000/μ L)
• During massive transfusions (see below)
• In acute Disseminated Intravascular Coagulation (DIC)
• Autoimmune thrombocytopenia
• In neonates if:
  o Platelets < 20,000 – 30,000/μ L
  o Platelets 30,000 – 50,000/μ L in neonates of low birth weight, with a coagulation disorder, during invasive procedures or with previous intraventricular or intraparenchymal cerebral hemorrhage
  o Platelets 50,000 – 100,000/μL
    ▪ in neonates with active bleeding

**Fresh Frozen Plasma**

Fresh Frozen Plasma (FFP) is primarily indicated to correct clotting factor deficiencies in patients with active bleeding for which specific factors are not available.²⁰

Transfusion with FFP is indicated for:²⁰

1. Congenital deficiencies of clotting factors (if there is no specific concentrate available) or for acquired deficiencies of multiple clotting factors if the prothrombin time (PT) or the activated partial
thromboplastin time (aPTT), expressed as a ratio of PT/aPPT, is greater than 1.5:

a. Continuous bleeding or the prevention of bleeding in patients with liver disease
b. Patients being treated with vitamin K antagonists, if major hemorrhage or intracranial bleeding is present or for emergency surgery. (Note: prothrombin complex concentrate is the treatment of first choice).
c. In patients with acute disseminated intravascular coagulation (DIC) and active bleeding.
d. For microvascular bleeding in patients during massive transfusion.
e. For deficiencies of single clotting factors.
f. Thrombotic microangiopathies (thrombotic thrombocytopenic purpura), hemolytic-uremic syndrome (HUS) or hemolytic anemia due to elevated liver enzymes and low platelet count (HELLP) syndrome
g. Hereditary angioedema

Other component transfusions will be discussed throughout this course activity as needed.

**Basic Principles Of Blood Transfusions And Pre-Transfusion Testing**

In the U.S., the Food and Drug Administration (FDA), regulates blood and blood components. Standards of practice and other guideline are written by
the American Association of Blood Banks (AABB) in cooperation with state and local health agencies as well as the American Red Cross.

Blood donors are screened by questionnaires and by a standard health interview and physical examinations which includes vital signs (temperature, heart rate (HR), respiratory rate (RR), blood pressure (BP) and a determination of the hemoglobin levels (Hgb) and often, the hematocrit (HCT) or “crit” — the packed cell volume (PCV) of the red blood cells (RBCs). There are a number of reasons that donors may be deemed ineligible to donate. It may be determined that the donor’s health may be harmed by donation, or, it may be determined that potential recipients may be harmed.

**Donor Requirements**

In general, an individual may not donate blood more than once every 8 weeks. An individual with a variety of medical or other conditions may not be allowed to donate blood or blood components either to protect their health or the health of potential recipients. Table 3 lists some reasons for denial to donate blood as determined by the American Red Cross.21

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Not eligible to donate</td>
</tr>
<tr>
<td>Bleeding disorder or coagulopathy</td>
<td>Individuals with Factor V deficiency who are not on anti-coagulants may donate. Individuals with other coagulopathies are evaluated on an individual basis. See medication list as well.</td>
</tr>
</tbody>
</table>

Table 3: Donor Requirements
<table>
<thead>
<tr>
<th>Condition</th>
<th>Eligibility Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis or jaundice</strong></td>
<td>Not eligible to donate if the individual had hepatitis or jaundice when older than 11 years of age.</td>
</tr>
<tr>
<td><strong>Heart disease</strong></td>
<td></td>
</tr>
<tr>
<td>- <strong>Angina</strong></td>
<td>Wait at least 6 months after anginal episode.</td>
</tr>
<tr>
<td>- <strong>Myocardial Infarct (MI)</strong></td>
<td>Wait at least 6 months following MI.</td>
</tr>
<tr>
<td>- <strong>Angioplasty or bypass surgery</strong></td>
<td>Wait at least 6 months after surgery or angioplasty</td>
</tr>
<tr>
<td>- <strong>Change in cardiac medications</strong></td>
<td>Wait at least 6 months after change to medications</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
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<tr>
<td><strong>5-α reductase inhibitors:</strong></td>
<td>Individuals must wait 6 months from the last dose.</td>
</tr>
<tr>
<td>- <strong>Avodart or Jalyn (dutasteride), Proscar (finasteride), and Propecia (finasteride)</strong></td>
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<tr>
<td><strong>Retinoids</strong></td>
<td>3 years post treatment</td>
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<tr>
<td>- <strong>Accutane, Amnesteem, Claravis or Sotret (isoretinoin), Soriatane (acitretin)</strong></td>
<td></td>
</tr>
<tr>
<td>- <strong>Tegison (etretinate)</strong></td>
<td>Not eligible to donate</td>
</tr>
<tr>
<td><strong>Aspirin, anticoagulants, anti-platelet medications</strong></td>
<td></td>
</tr>
<tr>
<td>- <strong>Aspirin or aspirin-containing medications</strong></td>
<td>No waiting period for donating whole blood. Individuals must wait 48 hours after taking aspirin or any medication containing aspirin before donating platelets by apheresis.</td>
</tr>
</tbody>
</table>
- **Coumadin (warfarin), heparin, Pradaxa (dabigatran), Xarelto (rivaroxaban) or Lovenox (enoxaparin) or other prescription anti-clotting agents.**
  - Plavix (clopidogrel)
  - Ticlid (ticlopidine)
  - Effient (prasugrel)
  - Feldene (piroxicam)

  Not eligible to donate.
  If medication is discontinued, the individual must wait 7 days before donating whole blood and 14 days before donating platelets by apheresis.
  For Feldene/piroxicam, if medication is discontinued, the individual must wait 48 hours before donating platelets by apheresis.

- **Hepatitis B Immune Globulin**

  Individuals must wait for 12 months post-treatment

**Hormone Treatments**

- **Bovine hormone treatments**

  Not eligible to donate

- **Human pituitary - derived growth hormone**

  Not eligible to donate

- **Hormone replacement therapy or oral contraceptives**

  Eligible to donate

**Pregnancy**

Wait until 6 weeks post-partum.

**Low weight**

Weight ≥110 pound

**High or low blood pressure**

BP≤180/100
BP≥80/50

**Age**

Donor must be at least 17 years old or if 16 years old, must have parental consent.

**Hemoglobin levels**

≥12.5g/dL

Whole blood and blood components, including fresh frozen plasma (FFP), cryoprecipitate, white blood cells (WBCs, buffy coat), immune globulins,
platelet concentrates are routinely tested for surface antigens, plasma antibodies and infectious diseases. Testing for antigens and antibodies is referred to as compatibility testing and is done pre-transfusion, unless there is an emergency need.

Electronic crossmatches are currently available at a growing number of transfusion centers and standard operating procedures (SOPs) developed for electronic crossmatching (EXM).\textsuperscript{22,23} The use of bar codes and automated systems have facilitated safety measures as well as the movement and tracking of blood and blood components across national and international borders.

The implementation of ration frequency identification devices is also being investigated and implemented in some areas to further improve the safety and availability of blood components.\textsuperscript{22} Flow cytometry, dynamic fluorescence imaging and patch-clamp measurements are increasingly used to detect cell surface antigens, incompatibilities and specific antibodies to various patient-specific and non-specific antigens.\textsuperscript{24-27}

**Current Guidelines for Pre-Transfusion Testing**

The following guidelines are obtained from the American Society of Hematology, shown in Table 4 below.\textsuperscript{9-12}

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Current Guidelines for Non-Emergency Recipient Testing**
<table>
<thead>
<tr>
<th><strong>ABO and Rh typing</strong></th>
<th>Determine ABO and Rh type</th>
<th>Recipient RBC tested with anti-A, anti-B, anti-D. Recipient plasma tested for type A₁ subgroup (most common) and B cells</th>
<th>25-30 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody Screening</strong></td>
<td>Screen recipient plasma for unexpected but clinically significant anti-RBC antibodies. If positive, the specific antibody should be identified</td>
<td>Use of standard non-ABO reagents</td>
<td>1hr</td>
</tr>
<tr>
<td><strong>If antibody screen is negative:</strong></td>
<td>Ensures ABO compatibility</td>
<td>Testing recipient plasma with sample of RBC from perspective donor</td>
<td>10 min</td>
</tr>
<tr>
<td><strong>Spin Crossmatch</strong></td>
<td>Ensures FULL serological compatibility between recipient’s plasma and RBC from perspective donor</td>
<td>Direct and Indirect Coombs test</td>
<td>1-1.5 hr</td>
</tr>
<tr>
<td><strong>If antibody screen is positive:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Full serological crossmatch</strong></td>
<td>Find compatible donors from inventory of donors with confirmed ABO/Rh status and who are negative for anti-RBC antibodies</td>
<td></td>
<td>15min.</td>
</tr>
<tr>
<td><strong>Electronic Crossmatch if available</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Blood and Blood Component Pre-Testing

Compatibility Testing

Karl Landsteiner described the ABO blood types in 1900. The ABO system describes antigens located on the membranes of the RBCs. These antigenic differences are based on different sugar residues — N-acetylgalactosamine for A-type antigens and galactose for B-type antigens. These isoantigens form the basis of blood compatibility testing and adverse transfusion reactions.

ABO and Rh0 (D) testing is carried out on donor blood. Other blood group systems are also checked. These other blood group systems include the MNS system, the Kell system and the Lewis system. In general, these systems are checked for specific, clinical purposes. For example, antibodies to the MNS system are occasionally seen in hemolytic transfusion reactions and in cases of hemolytic disease of the newborn.28

Maternal antibodies to Kell antigens can be very important in hemolytic disease of the newborn and critical in intrauterine transfusions.29-31

It is believed that the ABO system, along with the parallel system in WBCs (the Human Leukocyte Antigen (HLA) system)
evolved in large part as an adaptation to selective pressures placed by various infections, such as the malarial parasite, *Plasmodium*,\textsuperscript{32-34} bacteria and viruses.\textsuperscript{35} Alternatively, it is possible that these antibodies arose from a network of interactions between environmental antigens, microbes and the immune system.\textsuperscript{36}

**Overview Of ABO Inheritance**

Red blood cell membranes express a number of surface antigens. During immune development, these antigens induce an immune tolerance to “self” through “education” in the thymus and by various means, but antibodies against non-self antigens, isoantibodies or simply antibodies are also produced. Many of these antibodies are hemagglutinins, causing the RBCs which carry the isoantigens to clump together and, if complement binds, to hemolyze the RBC. The antibodies tend to be of the IgM class. IgM antibodies are pentameric and are the most efficient antibodies at inducing cross-linking and hemolysis.
**ABO System**

There are four blood groups in the ABO system, A, B, AB and O. Inheritance of the ABO blood group is controlled by a single gene, with three types of alleles. These alleles are \(i\), \(I^A\) and \(I^B\); \(I^A\) and \(I^B\) are inherited in a codominant manner with both \(I^A\) and \(I^B\) dominant over \(i\).

Type A RBCs have “A” antigen on their surface. Type B RBCs have “B” antigen and Type AB RBCs have both “A” and “B” antigens on their surface. Type O RBCs have neither “A” nor “B” on their surface but do have an antigen expressed — this is usually called the “H” antigen and can be thought of as common to the ABO system. Rare individuals who lack the “H” antigen have the “Bombay” blood group. This phenotype appears in less than 0.0004% of the population; and, these individuals, because they lack the “A”, “B” and “H” antigens, can donate RBCs to any individual but cannot receive any RBCs from any ABO donor. Type O blood is designated “\(ii\)”; type A is either \(I^AI^A\) or \(I^Ai\); type B is either \(I^BI^B\) or \(I^Bi\); type AB is \(I^AI^B\).

**Table 5: Inheritance of the ABO Blood Types**

<table>
<thead>
<tr>
<th>Blood Type of Mother</th>
<th>Blood Type of Father</th>
<th>O ((ii))</th>
<th>A</th>
<th>B</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>O ((ii))</td>
<td>(Ii)</td>
<td>1(^{\text{A}})</td>
<td>1(^{\text{A}})</td>
<td>1(^{\text{B}})</td>
<td>1(^{\text{A}})</td>
</tr>
<tr>
<td></td>
<td>TypeO</td>
<td>1(^{\text{A}})</td>
<td>1(^{\text{A}})</td>
<td>1(^{\text{B}})</td>
<td>1(^{\text{A}})</td>
</tr>
</tbody>
</table>

[28]
The Rh (for the Rhesus monkey in which it was first described) system is the other main blood grouping system important in transfusions. There are five antigens, but only the D antigen or Rh₀D is considered in blood typing.

The designation *Rh-positive* or *Rh-negative* refers to the presence or absence of the D-antigen, respectively. Immunization against the D-antigen occurs either through previous blood transfusions or *in utero*, that is if the mother is *Rh-negative* and the fetus is *Rh-positive*. Under these conditions, the mother responds to the Rh₀D antigen as non-self and makes antibodies (usually IgG antibodies) to the Rh₀D antigen. These antibodies then cross the placenta and can cause a hemolytic condition known as erythroblastosis fetalis or hemolytic disease of the newborn. Intrauterine transfusions (see

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below) may be necessary if these incompatibilities are not treated early. Pregnant women are routinely given anti-Rh\textsubscript{0}D antibodies (\textit{i.e.}, RhoGam\textsuperscript{TM}, BayRHo-D\textsuperscript{TM}, Gamulin Rh\textsuperscript{TM}) at 28 weeks gestation to suppress the response of an Rh-negative mother to the antigen expressed on the developing fetus.

**Overview Of Whole Blood Compatibility**

An individual with type A blood has the “A” antigen on the surface of the RBCs and antibody to the “B” antigen in their serum or plasma. Conversely, an individual with type B blood has the “B” antigen on the surface of the RBCs and antibody to the “A” antigen in their serum or plasma. An individual with type AB blood has both the “A” antigen and the “B” antigen on the surface of the RBCs and \textit{no} antibodies to either the “A” and the “B” antigen in their serum or plasma. An individual with type O blood has neither antigen on the surface of the RBCs and antibodies to both “A” or “B” in the serum or plasma. In addition, the Rh status is considered; the designation “Rh positive” indicates the presence of the Rh\textsubscript{0}D antigen and is indicated as “+”.

The “Rh negative” designation indicates the absence of the Rh\textsubscript{0}D antigen and is indicated as “-”. Rh+ blood should only be given to Rh+ individuals, but Rh- blood can be given to any patient.

In whole blood or packed RBC transfusions, only the antigens on the surface of the RBC are important for transfusion reactions because the cells are packed and washed and are essentially free of plasma (and therefore antibodies). So, an individual with Type O- blood is considered a universal blood donor and type AB+ is considered the universal blood recipient. Type AB+ plasma, because it has no antibodies, is considered the universal plasma donor.
People with type O blood do have surface antigen (the “H” antigen) but since this antigen is common to all blood groups, most people have no antibodies; these people have the rare Bombay blood type (hh) and can produce antibodies to the H antigen. These individuals can donate blood but can only receive transfusions from other hh donors.

**Table 6: Donor and Recipient Table.**

<table>
<thead>
<tr>
<th>Donor</th>
<th>A</th>
<th>B</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: Where there is a “✓”, the transfusion is considered compatible

**Pre-Transfusion Testing**

**Donor Blood**

Donor blood is pre-tested for ABO and Rh\(\_D\) antigens, the presence of antibodies and for markers of infectious disease. ABO typing determines whether the donor has A, B, O or AB type blood. Rh\(\_D\) testing determines the presence or absence of the Rh\(\_D\) antigen.

A number of tests are also performed to determine if the donor is infected with the Hepatitis B or C viruses, HIV-1 or HIV-2, human T-cell lymphotropic
viruses 1 and 2 (HTLV-1 or -2), *Treponema pallidum* (the causative organism for syphilis) and, more recently, for West Nile Virus.

Table 7: Donor Testing

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 and HIV-2 (If antibody +, infection confirmed by Western blot or immunoblotting)</td>
<td>Presence of antibody</td>
</tr>
<tr>
<td>HTLV-1 and HTLV-2</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B- core antigen</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C (if nucleic acid sequence test is +)</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Presence of specific nucleic acid sequences</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Presence of specific antigen</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td></td>
</tr>
</tbody>
</table>

*Recipient Testing*

The recipient is tested for ABO type, Rh\_0D type and for rare or unexpected antibodies to RBC surface antigens. This is considered essential because, the presence of antibodies in recipient serum, for example, to antibodies to other blood group antigens in the Kell(K) and Duffy (Fy) systems, can cause severe hemolytic transfusion reactions in the recipients. Maternal blood is
also tested for Kell and Duffy antigens to prevent hemolytic disease of the newborn.

**Figure 3: Direct Antibody Testing**

1. RBCs coated with antibodies (Y) to specific cell surface antigens
2. Anti-human antibody (Coombs reagent Y) is added.
3. RBCs agglutinate—the anti-human antibody (Y) cross-links with the antibody on the surface to clump the RBCs. \(\rightarrow\) POSITIVE DAT

**Figure 3: Indirect Antibody Testing**

1. Donor blood is mixed with a sample of the recipient’s serum.
2. If recipient serum has antibodies, they will bind to donor RBCs.
3. Anti-human antibody (Coombs reagent Y) is added.
4. RBCs agglutinate—the anti-human antibody (Y) cross-links with the antibody on the surface to clump the RBCs.
Screening of unexpected plasma or serum anti-RBC antibodies is through indirect antiglobulin testing (the indirect Coombs test is more commonly known as the Indirect Antibody Test or IAT). The direct Coombs test, or the Direct Antibody Test (DAT), screens for anti-RBC antibodies that are coating the RBCs. Both tests involve the use of anti-human globulin and checks for the presence of RBC agglutination. A full antibody titration may be done if a significant anti-RBC antibody is detected in the plasma of a pregnant woman or in the case of a patient with cold autoimmune hemolytic anemia (see below).

In acute situations, there may not be enough time to type the patient and cross-match the donor blood. Spin crossmatches, which are a shortened version of the complete test, may be used in emergency situations as can electronic crossmatching. In emergency situations, O- blood may be used as RBCs and AB- plasma may be used.

Crossmatching only provides minimal additional protection against incompatibility. After the major blood group antigens are screened, there are a large number of possible antigens that may cause incompatibility problems; and, the issue is which ones to screen. Without additional information to narrow down the search for potentially problematic antigens and antibodies, it would be like looking for the proverbial needle in the haystack.
Many hospitals are performing electronic crossmatches rather than the physical lab testing in patients who have a negative antibody screen. If the screening indicates significant levels of antibody, donor blood, which is *negative for that antigen*, is used. Also, in many cases a spin cross-match is used where the patient's serum is mixed with the donor cells and immediately placed into a centrifuge and spun. The absence of agglutination indicates ABO compatibility.

**Current Guidelines For Pre-Transfusion Testing Of Recipient Samples**

The following guidelines are obtained from the American Society of Hematology.\(^9\)\(^{-12}\)

*Pre-transfusion Blood Samples from the Intended Recipient*

The following are usually obtained from the recipient, if time and circumstances allow.

- Usually EDTA tube (plasma and red cells)
- Proper labeling of the sample includes:
  - 2 independent patient identifiers
  - Identity of the phlebotomist
  - Date and time of sample collection

  (Note: the blood sample is to be rejected without proper labeling as specified above).

- If the individual is a hospital inpatient or, if in past 3 months, the recipient has:
  - been pregnant
✓ been transfused
✓ uncertain history of either

and then the sample used can be up to 3 days old.

The sample tested can be older if the intended recipient has had outpatient pre-op testing as long as there is a negative history within the past 3 months; this may be significantly shorter, depending on hospital or institutional policy.

**Whole Blood And Blood Components For Transfusion**

Whole blood is generally no longer used in the U.S. because blood component therapy is equally useful and is believed to be more efficient particularly since one unit of whole blood can benefit more than one patient.

In recent decades, a number of procedures have been developed where an automated centrifuge device can separate out one or more types of cells from whole blood, returning the unneeded cells and fluids to the donor. The umbrella term is *apheresis* or *cytapheresis* — both may be used interchangeably.

Cytapheresis can include:
- Leukocytapheresis
- Plateletapheresis
- Erythrocytapheresis
- Thrombocytapheresis

Each of these removes the specific cellular component.
Apheresis is the removal of the acellular component of blood, the plasma, whereas cytapheresis is the removal of a cellular component.

**Packed Red Blood Cells (RBCs)**

Whole blood is spun in a large centrifuge and the platelet-rich plasma and buffy coat layer (WBC) is removed. The packed RBCs may be washed and filtered and are then essentially free of WBCs, plasma or platelets.

Packed RBCs are the component of choice to increase a patient’s hemoglobin levels. One unit of packed RBCs increases the Hb by ~ 1g/dL and increases the hematocrit (HCT) by ~3%.\(^9\)

Washed RBCs are commonly used for patients who may have been sensitized to plasma. This would include patients who have severe allergies, suffer from paroxysmal nocturnal hemoglobinuria or have received an immunization with IgA.

Washed and filtered packed RBCs are also used for patients with a history of non-hemolytic febrile transfusion reactions (see below), require CMV-negative blood and for an exchange transfusion, a cyclic procedure where the patient’s blood is slowly removed and replaced with an equal volume donor blood until the patient’s blood has been completely replaced. This procedure may be required in cases of sickle cell anemia crisis, Rh-induced hemolytic disease of the newborn, neonatal polycythemia, toxic drug overdose and severe jaundice.

**White Blood Cells (WBCs)**
White blood cells may be used in cases of persistent neutropenia (neutrophils <500/µL), particularly for sepsis that is resistant to antibiotic treatment. WBC transfusions are much less frequent as advances in drugs that stimulate granulocyte production have reduced the need.

**Platelet Rich Plasma (PRP)**

The plasma removed by centrifugation from the whole blood is platelet enriched and is used to prevent bleeding for situations where:

- Platelets <10,000/µL or severe thrombocytopenia
- Platelets < 50,000/µL or moderate thrombocytopenia with active bleeding
- Drug-induced platelets dysfunction with active bleeding
- Dilutional thrombocytopenia after transfusion
- Surgery if the circulation will be extracorporeal for ≥ 2 hours.
- Each unit of PRP increases the platelet count by approximately 10,000/µL and is usually sufficient to control bleeding in patients with thrombocytopenia without complicating factors or conditions. Approximately 50,000/µL is the goal in surgery to prevent excessive bleeding.

**Fresh Frozen Plasma (FFP)**

Fresh frozen plasma, or FFP, is deficient in platelets, but is a source of all clotting factors. FFP is not recommended for volume expansion, but is recommended for:
• Bleeding that is secondary to clotting factor deficiencies, particularly if the preparations of the specific factor are unavailable or if the specific deficiency is unknown.

• Multiple factor deficiency states — *i.e.*, disseminated intravascular coagulation [DIC], liver failure, or after a massive transfusion.

• Acute warfarin overuse or overdose to reverse the effects. This is a 2nd line option — Prothrombin Complex Concentrate (PCC) is the 1st line choice.

• In addition to packed RBCs if whole blood is not available for neonatal exchange transfusions.

**Cryoprecipitate**

Cryoprecipitate is a concentrated form of FFP and contains Factor VIII and von Willebrand’s Factor (~ 80 units each). Cryoprecipitate is also a source of fibrinogen (~250mg), ADAMTS13 (also known as von Willebrand factor-cleaving protease (VWFCP) which is deficient in congenital TTP), fibronectin and Factor XIII (fibrin stabilizing factor).

### Table 8: The coagulation factors

<table>
<thead>
<tr>
<th>Factor number</th>
<th>Descriptive name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>III</td>
<td>Thromboplastin, Tissue factor</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium (Ca²⁺)</td>
</tr>
<tr>
<td>V</td>
<td>Labile factor, Proaccelerin</td>
</tr>
<tr>
<td>VII</td>
<td>Proconvertin, Serum prothrombin conversion accelerator (SPCA), stable factor</td>
</tr>
<tr>
<td>VIII</td>
<td>Antihemophilic factor (AHF) or Antihemophilic globulin (AHG), Antihemophilic factor A</td>
</tr>
<tr>
<td>IX</td>
<td>Christmas factor, Plasma thromboplastin component (PTC), Antihemophilic factor B</td>
</tr>
<tr>
<td>X</td>
<td>Stuart–Prower factor, Stuart factor</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma thromboplastin antecedent, antihemophilic factor C</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor, contact factor</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin-stabilizing factor, (Fletcher factor), HMWK, high molecular weight kininogen</td>
</tr>
</tbody>
</table>

**Prekallikrein**

Works w/kininogen and Factor XII to activate Factor XI.

**Kininogen**

Works w/prekallikrein and Factor XII to activate Factor XI.
Immune globulins (immunoglobulins specific for the antigen in question) can be purified from collected sera and is used to produce concentrated supplies of anti-Rh₀D antibody.

Other specific immune globulins are available for cytomegalovirus, rabies, tetanus, hepatitis A and B, measles, respiratory syncytial virus, rubella, smallpox, and varicella virus. They are generally given intravenously (IV) and as such are referred to as IVIG. The use of immune globulins provides a passive protection against the virus or bacteria as opposed to a normal, active immune response where the individual’s immune system mounts a cellular, humoral (antibody) or both a cellular and humoral response to the invading pathogen. It is the treatment of choice for individuals who lack specific antibody and is used increasingly to treat autoimmune diseases such as:²⁰,³⁷,³⁸

- Idiopathic thrombocytopenic purpura (ITP)
- Kawasaki disease
- Guillain–Barré syndrome
- Myasthenia gravis
- Dermatomyositis

A recent Cochrane review has, however, recommended against using IVIG in neonates for either proven or suspected infections.³⁹

**Other Components**

Recent research has been focused on the development of blood substitutes to eliminate potential transfusion reactions. These are generally chemically inert substances, which have oxygen-binding (and releasing) capacity. Even
more recently, the emphasis has shifted to oxygen (O₂) therapeutics, focusing on restoring tissue oxygenation in specific tissues.

Currently, there are alternatives including hemoglobin-based O₂ carriers (HBOCs) and perfluorocarbon-based O₂ carriers (PFCOCs). Most of the current products have the disadvantage of short half-lives and significant adverse effects such as hypertension, gastrointestinal (GI) distress and higher than expected death rates in trauma patients. The PFCOCs appear to have fewer adverse effects.⁴⁰

Other alternatives include autologous transfusions (pre-depositing one’s own blood for transfusion for scheduled surgeries — this is known as preoperative autologous donation (PAD)), acute normovolemic hemodilution (ANH), where the patient donates their own blood immediately before surgery. Normal fluid volumes are maintained by the transfusion of colloids, such as albumin, dextrans or various starches or gelatins and crystalloids, such as normal saline and Ringer's lactate.⁴¹-⁴³ Free hemoglobin cannot be used because it is renotoxic.

Hematopoietic stem cells may be obtained from autologous (the patient) or from allogeneic (donor) sources for hematopoietic stem cell transplants. Colloids including albumin can be purified from blood and are transfused to help maintain fluid volumes, often in patients with sepsis.⁴⁴

Finally, coagulation factors may be transfused. These may involve the specific factors if these are known, or may involve the use of cryoprecipitate, a rich source of fibrinogen and many of the required coagulation factors in high concentrations.⁴⁵-⁴⁹
Transfusion Techniques

For red blood cell transfusion, at least a standard 18-guage needle should be used to prevent mechanical damage to the RBC from shearing or other physical forces. Needles larger than 18-gauge may be used if needed. Standard tubing filters should also be in place.

Other than sterile, isotonic saline (0.9%), no other fluid or drugs should be added to the infusion of any blood component. Ringer’s solution contains calcium ions (Ca$^{2+}$), which can cause spontaneous clotting, and either hypotonic or hypertonic solutions can damage and lyse the cells.

One unit of blood should take no longer than 4 hours for complete transfusion. If there is a clinical concern with too-rapid transfusion (such as concerns over heart failure, or hypervolemia) then single-donor blood may be divided into smaller aliquots (portions). This should be done under sterile conditions in the blood bank.

The procedure for dividing blood components into smaller aliquots is done routinely for transfusions in children, minimizing the risk of hypervolemia and transfusion reactions. If at all possible, these aliquots should come from a single donor, again, to minimize transfusion reactions and the exposure to multiple sources of new antigens and antigen sensitization reactions.

Observation of the Transfusion Patient

[42] nurseCe4Less.com nurseCe4Less.com nurseCe4Less.com nurseCe4Less.com
The transfusion patient should be closely observed, particularly during the transfusion itself and the first 15-60 minutes after the infusion of the blood components. Pulse, respiratory rate, heart rate, blood pressure and temperature should be observed and recorded and any significant observations regarding mental status, pain levels and fluid status (i.e., urine volume) should also be recorded and reported as needed.

The patient should be kept warm and covered to prevent chill from the environment, as these may be incorrectly interpreted as a potential transfusion reaction. Acute reactions to transfusion of RBCs and blood components may occur within the first 24 hours (acute) or over the following 1-14 days (delayed).

**Specific Indications For Blood Transfusions**

The specific indications for blood transfusions are discussed in this section relative to a medical condition or mechanisms of injury. Guidelines for transfusions under specific conditions are also reviewed.
Injury

Rapid Massive Hemorrhage

Massive acute hemorrhages, which may result from injury and/or the rupture of a major blood vessel, can result in anemia. Sudden loss of approximately 30% of the total blood volume can result in a fatal outcome, but with a less acute loss, approximately 60% of the total blood volume can be lost without fatality.

Treatment for acute blood loss consists of returning the patient to hemostasis, replacing blood volumes and the treatment of shock.

Injury by trauma of some form is the most common cause of death in those aged 1-44 years old. In general, trauma can be described as either blunt, involving a forceful impact to the body or or penetrating, involving a piercing or breakage of the skin.

As in all emergency situations, the ABCDE survey is the first priority. The ABCDE survey includes:

Airway
Breathing
Circulation
Disability
Exposure/environmental control

Regarding circulation issues and trauma, it should be noted that while external hemorrhage is always readily apparent, internal and potentially life-threatening hemorrhage is often not as obvious. The body compartments
with sufficient volume to allow significant internal bleeding are the chest, abdomen and the soft tissues of the pelvis.

External hemorrhage may be controlled by direct pressure. Internal hemorrhage may have to be treated surgically with the potential for autologous (autotransfusion) volume replacement using recovered blood. Internal hemorrhage can be detected if signs of shock are present, including tachypnea (decreased respiratory rate), intense sweating (diaphoresis), change in color or an altered mental alertness or status. Pulse and blood pressure measurements can also be key in alerting personnel to the potential for internal blood loss. Imaging studies can also be critical in detecting and determining the extent of the internal trauma and hemorrhage. These imaging studies include chest X-rays, CTs of the chest, abdomen, pelvis, spine, or head, and can be revealing.

Diagnostic peritoneal lavage (DPL) has been largely replaced as a diagnostic tool with a Focused Assessment with Sonography in Trauma (FAST), particularly for unstable patients. An Extended FAST (E-FAST) can also be performed. FAST and E-FAST is able to detect significant volumes of intraperitoneal blood.\textsuperscript{50,51}

Abdominal injury can constitute damage to the abdominal wall, the abdominal vasculature and either a solid organ such as the liver, spleen, kidney(s) or pancreas or to the stomach, the small or large intestines, colon, ureters or bladder. Grading scales may be used, ranging from Grade 1 (minimal damage) to Grade 5/6 for massive damage.

Hemorrhages in abdominal injuries may be immediate, especially in penetrating trauma where an abdominal vessel is directed impacted, or hemorrhages in abdominal injuries may be subtle, with low-volume blood
loss and few signs and symptoms of physiologic distress. Other causes of hemorrhage requiring transfusions are post-partum hemorrhages and trauma due to both blunt and penetrating injuries (\textit{i.e.}, explosions with shrapnel).

\textit{Current Guidelines for Emergency Release of Blood Products}

The following guidelines are obtained from the American Society of Hematology.\textsuperscript{9-12}

If an emergency situation exists, such as severe, ongoing and potentially life threatening hemorrhage or anemia, emergency release of blood products may be necessary. The recommendations in an emergency situation state:

- \textit{Notify blood bank of need for emergency release of RBC}
- \textit{Complete hospital’s “emergency release” form}
  - Document declaration of a transfusion emergency
  - U.S. federal regulations require 2 specific items on the form
    - Statement of the nature of the emergency (\textit{i.e.}, “massive GI hemorrhage”)
    - Signature of MD or “equivalent”; (PA, NP, RN, etc., cannot sign)

\textit{Send patient blood sample to blood bank as soon as possible (before emergency transfusion begins, if possible).}
What the blood bank will provide (depending on how much testing has already been performed):

- **Un-crossmatched RBC (ABO group-specific if determined on a current blood specimen)**
- **Group O RBC if blood bank has not documented patient’s ABO group on a fresh blood sample**
  - Rh negative depending on availability and hospital policy, if patient’s Rh status is unknown

The blood bank will retrospectively crossmatch all emergently issued units when it receives the patient’s testing sample and will begin issuing type-specific and crossmatched products when testing is complete.

**Chronic Hemorrhage**

Chronic blood loss or chronic hemorrhage may be due to bleeding tumors, including benign tumors such as rectal polyps or malignant tumors; heavy menstrual bleeding or gastrointestinal bleeds. Chronic bleeds can also occur in the brain, the eye or within any solid or hollow organ. Chronic blood loss can, over time, result in anemia, most often in an iron-deficiency anemia. Chronic bleeding can also occur with certain medications including anticoagulants (warfarin [Coumadin], heparin, rivaroxaban [Xarelto], dabigatran [Pradaxa]) and anti-platelet medications (aspirin, clopidogrel [Plavix], prasugrel [Effient]).
Bleeding and platelet disorders can also result in chronic hemorrhage — the most common include hemophilia, von Willebrand disease, idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), HELLP syndrome and Heparin-Induced Thrombocytopenia (HIT). Liver disease with inadequate production of coagulation factors can also result in chronic bleeding. Hypercoagulation syndromes such as disseminated intravascular coagulation (DIC) may result in the anemia and thrombocytopenia without blood loss.

Table 9: Bleeding disorders

<table>
<thead>
<tr>
<th>Class</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Platelet Disorders</td>
<td></td>
</tr>
<tr>
<td>Decrease in the absolute number of platelets</td>
<td>May be due to:</td>
</tr>
<tr>
<td></td>
<td>• Decreased production (<em>i.e.</em>, leukemias and myelodysplastic syndromes)</td>
</tr>
<tr>
<td></td>
<td>• Increased destruction (<em>i.e.</em>, in ITP, DIC, TTP)</td>
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<tr>
<td></td>
<td>• Increased sequestration by the spleen</td>
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<tr>
<td></td>
<td>• Drug induced (<em>i.e.</em>, by heparin, rifampin, sulfonamides, sulfonureas, quinidine)</td>
</tr>
<tr>
<td>Increase in the absolute number of platelets</td>
<td>* i.e., in essential thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td>* Thrombosis is more common than bleeding but may still result in anemia</td>
</tr>
<tr>
<td>Dysfunctional platelets</td>
<td>• von Willebrand’s disease</td>
</tr>
<tr>
<td></td>
<td>• Drug induced (<em>i.e.</em>, aspirin, NSAIDs)</td>
</tr>
<tr>
<td></td>
<td>• Systemic disorders (<em>i.e.</em>, uremia)</td>
</tr>
<tr>
<td>Coagulopathies</td>
<td></td>
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<tr>
<td>Acquired</td>
<td>• Vitamin K deficiency</td>
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</table>
### Traumatic Hemolytic Anemia

Traumatic hemolytic anemia can occur extravascularly, within the heart and intravascularly. Mechanical shear forces or turbulence causes hemolysis. The presence of schistocytes or abnormally shaped RBCs is diagnostic.

### Illness Due to Deficient Erythropoiesis

**Hypochromic-Microcytic Anemias**

Hypochromic-microcytic anemias where the RBCs are smaller and paler than normal may result from deficient erythropoiesis, the deficient production of RBCs in the bone marrow. This may result from deficient heme or globin synthesis. The microcytic anemias included in a differential diagnosis are iron deficiency, iron-transport deficiency and iron-
utilization deficiencies as well as the anemia of chronic disease (iron re-utilization anemia) and the thalassemias.

**Normochromic-normocytic Anemias**

Bone marrow failure results in a normochromic-normocytic anemia where the cells contain normal amounts of hemoglobin and therefore are normally pigmented (normochromic) and are normally sized (normocytic). Bone marrow failure may result from a lack of response to erythropoietin (EPO), a glycoprotein cytokine produced by the kidney.

Erythropoietin is believed to be regulated by a feedback mechanism based on the levels of oxygen in the blood and is produced by interstitial fibroblasts and peritubular cells of the renal cortex. Under hypoxic conditions, EPO is secreted and targets burst-forming unit-erythroid (BFU-E) cells expressing the EPO receptor, the colony-forming-unit-erythroid (CFU-E) cells, which maximally express the EPO receptor and proerythroblasts.

Erythropoietin cooperates with various other cytokines including interleukins-3 and -6 (IL-3, IL-6) glucocorticoids and others to stimulate pleuripotential stem cells. EPO has other non-hematopoietic roles such as stimulating angiogenesis and inducing the proliferation of smooth muscle fibers — the
actions for which EPO is well known as a “doping agent” in a number of endurance and professional sports.\textsuperscript{52,53}

Normochromic-normocytic anemias include the anemia associated with kidney disease, protein depletion and anemias associated with hypometabolic states (\textit{i.e.}, hypothyroidism and hypopituitarism). Aplastic anemia is a panhypoplasia where the precursors of the RBCs are affected along with platelet and white blood cell precursors resulting in a “triad” of anemia, thrombocytopenia and leukopenia. A normocytic-normochromic anemia is also seen in myelodysplastic syndromes, a group of proliferative disorders where blood cells are poorly formed, ineffective and abnormal cells, and in myelophthisic anemias where the bone marrow is replaced by non-hematopoietic cells.

\textit{Macrocytic Anemias}

The macrocytic anemias, defined as a mean corpuscular volume (MCV) of over 100fL/cell, can be megaloblastic or non-megaloblastic. Non-megaloblastic anemias form a diverse group of clinical states including anemias associated with chronic alcohol use and those associated with aberrant or abnormal cholesterol esterification by the liver. Megaloblasts are nucleated, large RBCs precursors — the nuclei of the megaloblasts show uncondensed chromatin.

Megaloblastic anemias result from defective DNA synthesis and the most common are caused by nutritional deficiencies of Vitamin B\textsubscript{12} and folate. B\textsubscript{12} and folate deficiencies can be due to poor diet, an increased utilization, inadequate utilization, increased excretion or inadequate absorption.
Vitamin B$_{12}$ for example, requires the presence of intrinsic factor (IF). Pernicious anemia or the presence of peptic ulcers can decrease B$_{12}$ uptake. In addition, the use of proton pump inhibitors (PPIs) used to treat gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) have recently been shown to be significantly associated with the risk of B$_{12}$ deficiency.$^{54}$ Similarly, folate antagonists such as methotrexate (used to treat various cancers or as an immunosuppressant) or triamterene (a K$^+$ -sparing diuretic used to treat hypertension) can induce a folate-deficiency associate megaloblastic anemia.

Hemolytic Anemias

Removal of senescent cells normally occurs at the end of the normal RBC lifespan of approximately 120 days. This is primarily done by the spleen, liver, bone marrow and by the reticuloendothelial system (RES). Hemolysis is the premature destruction of RBCs and can result from either extrinsic or intrinsic factors. The hemolysis may be extravascular, occurring primarily in the liver and spleen, or intravascular.

Extrinsic factors include hypersplenism (hyperactivity of the RES), autoimmune hemolytic anemia (cold, warm antibody or paroxysmal cold antibody, resulting in increased urinary hemoglobin levels) or by trauma and other mechanical injuries. Infections such as *Clostridium perfringens*, α- or β-hemolytic streptococci cause an extrinsic hemolysis due to toxin production where other infectious agents such as malaria (*Plasmodium*) species lyse the RBCs as part of the life cycle.
Intrinsic RBC membrane abnormalities may essentially induce an immune response resulting in hemolysis. Other membrane abnormalities may result in the destruction of the RBCs because of the resulting shape abnormalities (poikilocytosis) or size abnormalities (anisocytosis) cause a mechanical hemolysis within the smaller vessels (i.e., sheer stress). In addition to the membrane abnormalities that may result in hemolysis, disorders of RBC metabolism (Glucose-6-phosphate deficiency [G6PD]) and the hemoglobinopathies including sickle cell anemia (SCA) and thalassemias (α, β, and β-δ) may occur. Finally, either quantitative or functional abnormalities in membrane proteins including spectrin, ankyrin and actin can result in RBC hemolysis.

Autoimmune Hemolytic Anemias

In autoimmune hemolytic anemia (AHA), antibodies react with the RBCs with the subsequent binding of complement. The most common form of AHA is warm antibody hemolytic anemia. In warm antibody hemolytic anemia, the autoantibodies react with RBCs at 37° C or higher. These antibodies may occur spontaneously, associated with disorders such as systemic lupus erythematosus (SLE), lymphoma or with leukemias or they may appear as an adverse effect of drugs such as levodopa, cephalosporins, diclofenac and alpha interferon.55

Warm antibody hemolytic anemia is particularly important in the context of blood transfusion medicine because the presence of these warm antibodies makes the crossmatching of blood technically more difficult and increases the risk of a transfusion reaction (see below). In addition, the transfusion
recipient may develop, in addition to the autoantibodies already present, agglutinating (clumping) antibodies directed against the donor RBCs.\textsuperscript{56,57}

*Paroxysmal Nocturnal Hemoglobinuria*

Paroxysmal nocturnal hemoglobinuria (PNH) is a relatively rare genetic disorder where a stem cell membrane defect results in hemolysis and decreased WBCs and platelets. The RBCs are especially sensitive to complement and for reasons that are not well understood, hemolysis is increased during sleep. Anemia, leukopenia, thrombocytopenia and thromboses (both arterial and venous) are common and these events may occur episodically.

*Hereditary Spherocytosis and Elliptocytosis*

Poikilocytosis refers to variations in RBC shape and anisocytosis refers to variation in RBC size. Both may be seen in hereditary spherocytosis (HS) and elliptocytosis (HE), congenital RBC membrane disorders. HS and HE are autosomal dominant disorders with varying degrees of hemolysis (HS tends to have more hemolysis) and splenomegaly (more prominent in HE).

*Metabolic Disorders with Hemolytic Anemia*

Embden-Meyerhof Pathway Defects:

These are all autosomal recessive metabolic disorders in glycolysis pathways. Because they are autosomal recessive disorders, they only cause anemias in homozygous individuals, \textit{i.e.}, those carrying two copies of the defective gene. Pyruvate kinase deficiency is an example.
Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency:

This is an X-linked defect more common in African Americans but occurs also in people of Italian, Greek, Arabic and Sephardic Jewish ancestry. Hemolysis often occurs after an acute illness or taking oxidant drugs such as salicylates, some anti-malarials like primaquine, dapsone (used in the treatment of leprosy and as a 2nd line of treatment for pneumocystis in HIV+ patients) and sulfonamides.

**Hemoglobinopathies**

Normal adult hemoglobin (abbreviated HbA or α₂β₂) consists of four globular subunits with a central iron-binding heme group. The four subunits consist of 2 α chains and 2 β chains. Normal infant Hb (HbF) has 2 α chains and 2 γ chains (α₂γ₂). As the infant grows and RBCs are replaced, the γ chains are gradually replaced with adult-type β chains.

Another form of hemoglobin contains 2 δ chains along with 2 α chains and is known as HbA₂ or α₂δ₂. HbA constitutes 97% of normal adult hemoglobin while HbF and HbA₂-2 constitute approximately 3%. Hemoglobin carries oxygen from the lungs to the rest of the body tissues. It can also carry carbon dioxide (CO₂) and besides the RBC is found in macrophages, the substantia nigra (in dopaminergic neurons), astrocytes, oligodendrocytes and in alveolar cells. The different hemoglobinopathies represent abnormal variations in Hb structure.
Sickle Cell Anemia

Sickle Cell Anemia (SCA) is an autosomal recessive defect where a single nucleotide polymorphism (SNP) causes an A → T alteration in the DNA sequence. This results in the substitution of a glutamic acid by a valine, producing an HbS. The HbS, under hypoxic (low oxygen) conditions induces polymerization by the Hb with subsequent crystallization and the deformation and eventual hemolysis of the RBC.

Acute exacerbations, known as crises, can be precipitated by acute illness, fever, viral infection or trauma, though often, they appear spontaneously or for no known reason. These crises can be painful, with severe oxygen deprivation (infarction) occurring in the bones, spleen, lungs and/or kidneys. A common cause of mortality in SCA is acute chest syndrome with microvascular occlusions accumulating in the lung tissue. Aplastic crises can occur as well. Signs and symptoms include anemia, jaundice, pallor, hepatosplenomegaly, cardiomegaly, systolic ejection (flow) murmurs, cholelithiasis (gallstones) and chronic ulcers around the ankles (punched-out ulcers).

Thalassemias

The thalassemias are characterized by defective hemoglobin synthesis and produce a microcytic hemolytic anemia, and are an inherited disorder. Thalassemias are the most common hemoglobinopathy and results from the decreased or abnormal production of one of the four hemoglobin subunits — α, β, γ, or δ. The types of anemias are most common in individuals of Mediterranean, African and Asian ancestry. Iron overload can be the result of
multiple transfusions. Signs and symptoms include anemia, hemolysis, splenomegaly and bone marrow hyperplasia.

The condition β-thalassemia is the result of decreased production of the β chain. Homozygotes (β thalassemia major) can be severely anemic and show signs of bone marrow hypertrophy. Heterozygotes (β thalassemia minor) are much less severely affected and are either asymptomatic or present showing signs of mild or moderate anemia.

The other condition of α-thalassemia results from a defect in the production of the α chain, but since 4 genes are involved in α chain production, there are 4 sub-types, depending on the number of genes affected.

- Single-gene defect: α-thalassemia-2. These individuals are usually asymptomatic.
- Two-gene defect: α-thalassemia-1. These individuals carry the train and may have a mild to moderate microcytic anemia.
- Three-gene defect: A three-gene defect results in hemoglobin with excess β chains (HbH). In infants, the excess β chains are paired with γ chains to produce Bart’s Hb. Individuals with the three-gene defect have a hemolytic anemia often accompanied by splenomegaly.
- Four-gene defects are fatal in utero.

Other Hemoglobinopathies

Other hemoglobinopathies include the following:
• Hemoglobin C is more common in African Americans and has similar but milder features as SCA.
• Hemoglobin S-C combines the S- and the C- Hb defect and is again more common in African Americans. Symptoms tend to be less severe than in SCA, but hematuria, retinal hemorrhages and aseptic necrosis of the femoral head are common.
• Hemoglobin E occurs primarily in those of African or Southeast Asian descent and is an autosomal recessive disorder. Homozygotes for HbE are most often treated with chronic transfusions.

Complications Of Transfusions: Part I

This section covers current guidelines for principles for the transfusion of incompatible RBC in an emergency release of blood products or in the case of mismatch. The following guidelines are obtained from the American Society of Hematology.\(^9-12\)

Clinically, the scenario of severe warm or cold autoimmune hemolytic anemia can occur where the patient has auto-antibodies which react with all of the blood bank’s reagent cells. Alternatively, the blood bank may not be able to determine if alloantibodies are present or none of the currently available RBC unit is compatible. In this type of scenario, a clinical decision must be made if the risk of an incompatible RBC transfusion outweighs the likelihood of death. In these types of situations, the American Society of Hematology has produced the following principles:
Communication between bedside clinician and transfusion service physician is essential.

- **Obtain careful history of prior transfusion or pregnancy:**
  - If history negative, probably safe to transfuse ABO-compatible RBC
  - If history positive or uncertain, assess risk: benefit of delaying transfusion to complete testing
- **Assess how long it may take for blood bank or reference lab to complete pre-transfusion testing**
- **Agree on best approach to choosing among incompatible RBC units (transfusion physician will advise)**
- **Attempt to mitigate need for immediate transfusion: bed rest, oxygen.**
- **Ultimately, do not deprive a patient with autoimmune hemolytic anemia of a needed, lifesaving transfusion.**
- **Autoantibody will shorten survival of transfused RBC and patient’s endogenous RBC to a similar extent.**
- **Most undetected alloantibodies will cause delayed hemolytic transfusion reactions:**
  - May be misdiagnosed as worsening of autoimmune hemolysis
  - Not usually life-threatening
- **Bedside team must be hypervigilant for acute intravascular hemolytic reaction during transfusion.**
- **The most serious transfusion reactions include:**
  - Acute hemolytic transfusion reactions
  - Acute respiratory distress and lung damage
  - Circulatory (volume) overload

[59]
Early recognition of the signs and symptoms of serious transfusion reactions is critical. These should not be confused with the more common and much less severe reactions, which include febrile but non-hemolytic reactions and chills alternating with rigor (chill-rigor reactions). However, if the febrile or chill-rigor reactions occur during the transfusion, the transfusion should be halted immediately, with the IV line kept open with isotonic saline. The blood component should be immediately returned to the blood bank along with a sample of the patient’s anti-coagulated blood for the blood bank to examine. Unless there is an emergency situation (and O- RBCs may then be used), the transfusion should be halted until the cause of the transfusion reaction can be determined.

Other reactions that can signal a transfusion reaction include:

- Dyspnea or any difficulty breathing
- Light-headedness
- Urticaria (unless localized)
- Significant itching (unless localized)
- Flank or lumbar pain
- Facial flushing

**Acute Hemolytic Transfusion Reactions (AHTR)**

While acute hemolytic transfusion reactions (AHTR) are relatively rare, they are serious and the nursing and hospital staff should be alert to the possibilities.

*The most common cause of AHTR is human error.*

Mislabeling of the patient’s pre-transfusion sample Failure to check and confirm that the blood component is intended for a particular patient.
The most common cause of AHTR is human error; the mislabeling of the patient’s pre-transfusion sample or failing to check and confirm that the blood component is intended for a particular patient.

In most AHTRs, it is usually the donor cells that are hemolyzed by the recipient’s immune system. This can result from ABO/Rh incompatibilities, antibodies passively transfused by plasma that has not been fully removed from the packed RBCs, the presence of fragile RBCs or fragments of RBCs resulting from overheating, mechanical forces or by the inadvertent introduction of hypotonic solutions.

In AHTR, the hemolysis is intravascular. It may be accompanied by hematuria, depending on the condition of the patient’s kidneys. AHTR may also be accompanied by disseminated intravascular coagulation (DIC). The severity of the AHTR depends in large part on the patient’s overall condition, condition of their heart, liver and kidneys, the degree of ABO/Rh incompatibility, whether that patient has been sensitized previously, the amount of blood component transfused and the administration rate of the blood component.

If there is an acute reaction, it most commonly happens within 60 minutes of the initiation of the transfusion. Onset of the reaction is usually abrupt with the patient (if conscious) complaining of discomfort or anxiety. Other symptoms include dyspnea, fever, chills, chill-rigor reaction, and flushing of the face and flank or lumbar (low back) pain.

If the patient is unconscious or under anesthesia, the primary sign may be hypotension (low blood pressure), uncontrolled bleeding from the incision or site of injury or gross hematuria. If DIC is present, bleeding from the mucous membranes may be observed as well. Shock may ensue, with a
rapid, feeble pulse, hypotension, cold and clammy skin and nausea or vomiting. Jaundice may also appear, but is often difficult to detect in the early stages.

Steps to be taken immediately if AHTR is suspected

- Re-check patient wristband or ID and re-check the blood component identification label.
- Notify the blood bank and supervisory personnel as well as the physician responsible for the patient.
- Stop the transfusion.

After the transfusion has been halted, supportive treatment can begin. Initially, supportive treatment should consist of achieving and maintaining adequate blood pressure and renal blood flow. Adequate renal blood flow is necessary to fully remove the hemoglobin and to maintain renal function. Both blood pressure and renal function are addressed with IV isotonic (0.9%) saline and furosemide.

The prognosis is generally good if diuresis and decreasing blood urea nitrogen (BUN) are seen. A poor prognosis is indicated by long-term oliguria and shock. If oliguria (decreased urine volume) is observed after the first 2-3 hours after supportive therapy is begun, a nephrologist should be

Supportive Treatment May Include:

- IV normal saline to maintain urine output at > 100mL/hr for the first 24 hours.
- Initial dose of furosemide:
  - Adults: 40-80mg
  - Children: 1-2 mg/kg
consulted as soon as possible because of the possibility of acute tubular necrosis.

Free hemoglobin in the plasma and urine (hemoglobinuria) along with low haptoglobin levels is diagnostic of AHTR.

**Delayed Hemolytic Transfusion Reactions**

Delayed hemolytic transfusion reactions may be quite common, but are often not clinically identified because the reactions are usually mild and in general, appear to be self-limiting. These delayed reactions may be the result of pre-sensitization to RBC antigens. The only symptoms may be a slight fever. Lab tests may reveal a lower hematocrit and possibly an increase in bilirubin and LDH. Gross hematuria is rare.

**Acute Respiratory Distress and Lung Damage**

Acute lung damage is relatively rare, but accounts for the most common cause of death in transfusion reactions. The pathophysiology of the damage is due to the presence of anti-HLA or anti-granulocyte antibodies in the donor plasma; these antibodies attack the WBC (which carry the HLA antigens) and both agglutinate and cause degranulation of recipient granulocytes in the lung tissue. Acute respiratory distress may result. Chest X-ray shows a characteristic non-cardiogenic pulmonary edema. However, most cases of acute lung damage show mild symptoms and are likely often missed, though all suspected cases should be reported.
The use of blood products donated by never-transfused men or never-transfused women who have never been pregnant decreases the risk of any acute transfusion reaction because it is unlikely that these individuals have been sensitized to other human antigens, such as RBC or HLA antigens. (See section on TRALI below).

**Circulatory (Volume) Overload**

Volume overload, especially if the transfusion occurs too rapidly, is a real and present danger, though historically, it has been under-recognized and under-reported. Recent studies have indicated that volume overload is the second most common cause of death in transfusion reactions reported to the FDA.

Patients at risk for volume overload are those with pre-existing (though not necessarily recognized) cardiac, respiratory and renal insufficiency. Those at risk include the elderly and neonates. Blood components are highly concentrated and can provide a high osmotic load, forcing fluids (by osmotic pressure gradients) into intravascular spaces.\(^{58-61}\)

Signs and symptoms of volume overload include dyspnea, the presence of respiratory crackles, coughing, edema in the extremities, tachycardia, and irregular heart rate and increased blood pressure. (See sections on TRALI and TACO below).

If any of these symptoms are noted, the transfusion should be stopped immediately and the supervisory staff and medical personnel should be notified. Treatment is supportive, as used for heart failure, including the use of 20 – 40 mg of furosemide (IV). If the patient was undergoing a plasma
transfusion (using fresh frozen plasma, for example) to reverse a warfarin overdose, furosemide at a lower dose may be given, but the preferred treatment is with a prothrombin complex concentrate (PCC). If pre-existing heart failure or renal failure is known in a transfusion patient, furosemide is given prophylactically at 20 – 40 mg (IV).

Aggressive volume expansion — essentially a volume overload — is recommended in kidney transplantation, whether it is for chronic renal failure or for other indications such as hypertension, ischemic heart disease, and chronic heart failure. However, more recent results indicate that it may not be necessary to maximize the function of the transplanted kidney(s). Recent results indicate that a less aggressive approach, with lower volumes resulted in similar good results.

Other Transfusion Reactions

Altered Oxygen Affinity

The affinity for oxygen in RBC is to a large part dependent on the hemoglobin, but levels of RBC 2,3-diphosphoglycerate (DPG) play a role as well. RBC 2,3-diphosphoglycerate decreases in RBC blood products stored for over 7 days and is at negligible levels after 10 days of storage. This decrease in DPG has the effect of increasing hemoglobin affinity for oxygen, and this increase in affinity or attraction for oxygen has the effect of decreasing the amount of oxygen eventually released to the tissues. This can be an important factor for exchange transfusions in infants, and patients in sudden cardiac arrest in acute crisis (acute chest syndrome, stroke) and
with severe heart failure. Using fresh packed RBC in these cases is recommended.

**Graft-Versus-Host Disease**

Graft versus Host disease (GVHD) occurs when immune cells from the donor (the “graft”) recognized the recipient (host) as being foreign, or carrying foreign antigens on the surface of host cells. The grafted cells then attack the host cells.

In general, for GVHD to occur in a transfusion or in any transplantation, three criteria known as the Billingham criteria\(^{63}\) must be met:

- The donor cells must be immune-competent. This occurs when functional WBCs containing T-cells and possibly B-cells are transferred.
- The recipient shows immunological differences from the host and is histo-incompatible (major or minor histocompatibility mismatches can occur).
- The recipient is immunocompromised and incapable of rejecting the transplanted cells.

Acute GVHD can occur anytime before 100 days post transfusion (or transplant) while chronic GVHD occurs after the 100-day period, those these definitions may be altered by the current work of the National Institutes of Health (NIH) chronic GVHD consensus project working group. Commonly, GVHD occurs between 4 - 30 days after transfusion of blood components.

The severity of the GVHD is graded by the modified Glucksberg criteria. These criteria are based on the appearance of fever, a centrifugally spreading maculopapular erythematoso skin rash (sometimes with bullae),

\[66\]
gastrointestinal symptoms (usually vomiting and/or a bloody diarrhea), lymphadenopathy, pancytopenia and changes in liver function as measured by the appearance of jaundice and increased bilirubin levels. Acute damage in GVHD is the result of donor T-cell activation followed by the production of a variety of inflammatory cytokines (a cytokine storm) including gamma interferon (IFN-γ), Tumor Necrosis Factor-α (TNF-α) and Interleukins 1, 2, 6 and 12 (IL-1, IL-2, IL-6, IL-12). These inflammatory cytokines along with the presence of natural killer cells (NK cells) and cytotoxic T lymphocytes (CTLs) directly and indirectly induce host cell damage and death.\textsuperscript{64}

Graft versus host disease is rare in transfusion medicine, particularly if blood components are irradiated to irreversibly damage the graft (donor) lymphocytes. Irradiation of transfused blood components is strongly recommended if the recipient is:

- **Immunocompromised:**
  This can include neonates or patients with:
  - Congenital immunodeficiency syndromes
  - Hematologic cancers
  - Hematopoietic stem cell transplants
- **A 1\textsuperscript{st} degree relative of the donor**
- **When HLA- bearing blood components are transfused.** In practice, this means WBCs, but it should be remembered that WBC could contaminate the packed RBCs or PRP components.

While rare in transfusions, GVHD has a >90% mortality because there is no specific treatment available. Prevention by careful screening, checking to ensure that the correct blood components are being transfused to the correct individual and using irradiated blood components as recommended

[67]
has reduced the incidence of GVHD. However rare the incidence, vigilance is required because GVHD as an adverse reaction to a transfusion is nearly always fatal.

Complications of Massive Transfusions

Massive transfusion can be defined as the transfusion of greater than or equal to an individual's total blood volume within a 24-hour period. This represents approximately 10 units of blood. Recent advances have been made in battlefield hospitals. The use of rapid infusers allow the transfusion of pre-warmed 250 mL and 500 mL boluses (rapid infusion) of blood and can be mixed with FFP; this has resulted in great clinical advantage for severely traumatized soldiers. These battlefield advances also involve the concomitant use of hemostatic agents such as Tranexamic acid (TXA).

The main issue in massive transfusions is that during the process of transfusing a large volume of colloidal RBCs along with crystalloid fluids such as Ringer's lactate or isotonic saline, the clotting factors within the plasma and the platelets transfused in the FFP, cryoprecipitate and/or PRP are diluted and a dilutational coagulopathy is induced. In addition, under conditions where the massive transfusion is given for massive accidental blood loss, there is a “consumptive” coagulopathy occurring as well — that is, the coagulation process is consuming the coagulation factors at a rate faster than can be replaced. All this can lead to what has been termed a “lethal triad” of acidosis, hypothermia, and bleeding. Research over the past few years has indicated that the administration of high ratios of plasma to packed RBC can improve mortality and is known as “damage control
resuscitation”. Overall, the data is indicating improved mortality by using RBC, plasma and platelets in a 1:1:1 ratio.

Hypothermia can be avoided by using heat-exchange devices to gently warm the blood components before it enters the recipient. Alternative warming devices such as microwave ovens or heating pads are not recommended because of the potential for damage to the RBCs, hemolysis and uneven warming.

Citrate toxicity is a concern for patients with poor liver function. Patients with poor renal function may be at risk for hyperkalemia (high potassium levels) if the blood components used have been stored for longer than one week. Hypocalcemia (low calcium levels) has also been observed, and must be adjusted accordingly. All these potential toxicities are increased with hypothermia, increasing the importance of using appropriate warming devices and transfusing blood components as slowly as is clinically feasible.

Protocols are currently being developed where the FFP and PRPs are given earlier in the transfusion procedure before any coagulopathy develops. Early results are indicative of decreased mortality and morbidity, but recommendations have not yet been announced. Current recommendations are that for every unit of blood given, one unit each of plasma and platelet concentrates should be given.

**Infections Resulting from Transfusions**

While blood and blood components are screened for a variety of pathogens and while every effort is made to minimize contamination, there is an inherent risk of infections arising from transfusions. The list of pathogens for which all blood in the U.S. is screened is given in Table 7. They include HIV-
1 and HIV-2, HTLV-1 and HTLV-2, Hepatitis B and C, West Nile Virus and *Treponema pallidum* (the causative spirochete in syphilis). However, this is only a partial list and does not include new and evolving pathogens or more rare pathogens. Part of this potential for infection is screened out at the donor stage using the general health questionnaires and part is screened by pre-testing donor samples. Clearly, if a pathogen is not tested for or not screened or asked about during the patient evaluation, the risk of infection remains.

The best approach to infections in the transplant patient is to maintain proper protocols and follow proper sterile procedures in addition to being aware of the possibilities and remaining vigilant in the constant monitoring of transfusion patients.

*Bacterial Infections*

Current protocols for blood collection, storage and transfusion have resulted in a decrease in the risk of bacterial contamination and infection from packed RBC. Nonetheless, packed RBC should be inspected for any color change, indicative of bacterial growth. Cryophilic (cold-loving) organisms such as *Yersinia spp.* may contaminate packed RBCs and produce significant levels of endotoxin. Rarely, syphilis has been transmitted in fresh blood products and platelets. Pre-testing will not detect antibodies early in the infection, and it is presumed that these cases occurred because the donors were seronegative at the time of donation.

*Viral Infections*

- Hepatitis:
The risk of hepatitis (A,B,C,E) transmission has been reduced by the combination of pre-screening, pre-testing and by the inactivation (heat treatment) of blood components. Recombinant technologies have been used to produce purified and sterile coagulation factors; in the past, treatment of coagulopathies was an important cause of hepatitis infections.

- **Human Immunodeficiency Virus (HIV):**
  Pre-testing and screening for both HIV-1 (more common in the U.S.) and HIV-2 is done on all donor blood products. Testing for both antibodies to HIV and for the genetic material (nucleic acid testing) for HIV-1 and -2 are done to minimize the risk. Finally, potential blood donors are screened for high-risk behaviors before they are accepted as blood donors. Since the late 1980s, this combination of approaches has greatly reduced the risk of HIV transmission via blood products.

- **Cytomegalovirus (CMV):**
  Cytomegalovirus can be transmitted in WBC-containing components. CMV is a ubiquitous virus and will not, in general, cause disease in an immunocompromised recipient. However, CMV can be a serious problem for immunocompromised patients. In these cases, WBC-depleted blood components can be given. Alternatively, CMV-negative donors should be used. This alternative is somewhat more difficult to achieve given the widespread nature of CMV.
• Human T-cell lymphotropic virus 1 and 2 (HTLV-1 and HTLV-2):
  HTLV-1 (also known as adult T-cell lymphoma virus type 1 or adult T-cell
  leukemia lymphoma (ATLL)) is associated with adult T-cell
  lymphoma/leukemia, HTLV-1–associated myelopathy, and tropical
  spastic paraparesis. It was originally thought that HTLV-2 was
  associated with Hairy Cell Leukemia, but this has not been proven
  valid. Nevertheless, all donor blood is tested for both HTLV-1 and
  HTLV-2 antibodies.

Prion Disease and Malaria

• Prion Disease:
  Concern for the transmission of the prion disease, Creutzfeldt-Jakob
disease (mad cow disease), is the reason that individuals who have
lived for significant time periods in the United Kingdom (UK) and some
other parts of Europe where mad cow disease were detected are not
allowed to donate blood in the U.S. This denial stands even though
Creutzfeldt-Jakob disease has never been reported as transmitted by
transfusion, or the prions detected in blood components.

  Prevention of potential prion transmission is also the rationale behind
not allowing blood donations from individuals who have in the past
received human-derived growth hormone, a dura mater transplant or
anyone with a family member with Creutzfeldt-Jakob disease.

Malaria:

  Prospective donors are, by requirement, asked about malarial
  symptoms and travel to areas where malaria is prevalent because the
  malarial parasite can be easily transmitted through RBCs. Malaria can

[72]
be latent and many people are unaware that they are infected. Donors with a previous diagnosis of malaria are asked to wait for 3 years after successful treatment while those who have visited areas of the world where malaria is endemic must wait for one year and be symptom-free.

Newer or rarer pathogens do appear in blood products and components. Chikungunya virus has appeared in Europe and North America recently\(^70\) and the parvovirus, human erythrovirus B19 has been reported in increasing numbers as well.\(^71,72\) In addition, septic infections may be associated with other serious complications of transfusions.\(^73\) Finally, tropical and parasitic diseases can appear in blood, blood products and result in infections and sepsis.\(^74\)

**Therapeutic Apheresis**

Therapeutic apheresis may be defined as “the separation of whole blood into its major components and removal of the abnormal, pathogenic component.”\(^75\) There are a number of different types of therapeutic apheresis including:

- Plasmapheresis (Plasma exchange)
- Leukocytapheresis (removal of white blood cells)
- Thrombocytapheresis (removal of platelets)
- Erythrocytapheresis (removal of red blood cells)
The terms apheresis, plasmapheresis, therapeutic plasma exchange and cytapheresis are used interchangeably by many even though they describe different procedures.

**Apheresis:** Technically, this term refers only to the removal of whole blood for extracorporeal processing.

**Cytapheresis:** The removal of whole blood, separation into components, *removal of cell fractions* and the re-infusion of remaining cells.

**Therapeutic Plasma Exchange:** The removal of whole blood, separation into components, *removal of plasma* and the re-infusion of cells. Therapeutic plasma exchange (TPE) is also referred to a Therapeutic apheresis. Plasma is not re-infused, but substituted with a purified blood component such as FFP to prevent hypovolemia.

**Plasmapheresis:** The removal of whole blood, separation into components, *removal of plasma* and the re-infusion of cells. Plasma is not re-infused, but substituted with a purified blood component such as FFP to prevent hypovolemia.

Therapeutic apheresis is considered very safe, though there are some risks to using large bore IV catheters and citrate anticoagulants, which may negatively impact Ca²⁺ levels and risks associated with the movement of fluids into intravascular spaces. Close observation of the patient and rapid response if adverse reactions are noted is normally all that is required.

**Modalities Used in Therapeutic Apheresis**

- Cytapheresis
o Cell removal and/or replacement
  ▪ Erythrocytes (sickle cells, etc.)
  ▪ Platelets (thrombocytosis)
  ▪ Leukocytes (leukemia, ECP)
o Leukocyte collection
  ▪ Stem cells
  ▪ *ex vivo* (extracorporeal) immune modulation

- Hemoperfusion:
  Hemoperfusion refers to the passage of anti-coagulated blood through material that has particles of specific properties adsorbed to it. Specific components of the blood will adsorb to the particles, removing those components from the blood. Examples include charcoal (to remove poisons, drugs or toxins), resins to remove lipid-soluble drugs, antigen- or antibody-coated particles to remove specific antibodies or antigens, respectively, and, antibiotics (*i.e.*, polymyxin B) to remove specific endotoxins. Adsorption to the particles can be:
  o Hydrostatic
  o Ionic
  o Antibody mediated
  o Combinations/other

- Leukocytapheresis:
  o Selective filtration
  o Fcγ adhesion

- Plasmapheresis:
Superflux Hemofiltration - primarily used in nephrology. Similar to hemodialysis
  - Albumin is used as substitute to replace protein

Single filtration/centrifugation - blood is passed through one filter and one round of centrifugation
  - Plasma removal
  - Albumin is used as substitute to replace protein
  - FFP may be used as a substitute
  - Combinations

Cascade filtration - blood is passed through a series of filters
  - Albumin is used as substitute to replace protein

Filtration with Adsorption
  - Albumin is used as substitute to replace protein
  - Precipitation of drugs, toxins, poisons
  - Combinations

Biological devices
  - Albumin is used as substitute to replace protein

Apheresis techniques may be manual or automated. Centrifugation is based on the separation of blood components based in mass, size and specific gravity while elutriation techniques are based on differences in cellular size.

Figure 4: A centrifuged test tube showing the various layers
**Plasma Exchange**

Therapeutic plasma exchange (TPE) replaces patient plasma with, preferably, a 5% albumin solution and returns RBCs, WBCs and platelets. The 5% albumin solution is preferred because it carries a lower risk of infection and adverse reactions. Fresh frozen plasma (FFP) should be used in place of the albumin solution for patients with thrombotic thrombocytopenic purpura.

Therapeutic plasma exchange can be compared to dialysis, but, it can also accomplish what dialysis cannot, which is the removal of protein-bound drugs and toxins. A single-volume exchange can remove up to 66% of protein-bound toxin such as toxic shock syndrome toxin-1 and shiga-toxin.\(^{76-78}\) The American Society for Apheresis currently recommends plasma exchange as 1\textsuperscript{st} line therapy for:\textsuperscript{12}

- ANCA-mediated rapidly progressive glomerulonephritis (Wegener's granulomatosis)
  - On dialysis
  - With diffuse alveolar hemorrhage
- Antiglomerular basement membrane antibody disease (Goodpasture's syndrome)
  - On dialysis
  - With diffuse alveolar hemorrhage
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Cryoglobulinemia (severe)
- Focal, segmental glomerulosclerosis (recurrent)
- Guillain-Barré syndrome
- Hemolytic-uremic syndrome (HUS)
- Atypical: due to autoantibody to factor H
- Hyperviscosity in monoclonal gammopathies
- Myasthenia gravis
- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections)
- Paraproteinemic polyneuropathy with IgG/IgA, IgM
  - With or without Waldenström's macroglobulinemia
- Renal transplantation, antibody-mediated rejection
- Sydenham's chorea
- Thrombotic thrombocytopenia purpura
- Fulminant Wilson's disease

The American Society for Apheresis currently recommends plasma exchange as 2nd line therapy, either alone or in combination with other treatment(s) for:

- ABO incompatible stem cell or kidney transplant
  - The recipient may be treated with therapeutic plasma exchange
- Anemia, pure red cell aplasia
- Catastrophic antiphospholipid syndrome
- Autoimmune hemolytic anemia
  - Cold agglutinin disease, if life threatening
- Hemolytic-uremic syndrome, due to complement factor gene mutation
- Lambert-Eaton syndrome
- Multiple sclerosis
  - If acute and unresponsive to corticosteroids
- Myeloma (cast nephropathy)
- Neuromyelitis optica
- Phytanic acid storage disease (Refsum's disease)
- Rasmussen's encephalitis
- Red cell alloimmunization in pregnancy
  - If intrauterine transfusion is not available
- Renal transplantation
  - Desensitization to a living donor
  - Due to donor-specific HLA (Human Leukocyte Antigen antibody)
- System Lupus Erythematosus (SLE)
  - Severe (i.e., cerebritis, diffuse alveolar hemorrhage)

The American Society for Apheresis currently has determined that the role of therapeutic plasma exchange has not yet been defined and any decision to treat with TPE should be made on an individual basis. Institutional Review Board (IRB) approval should be obtained.12

- Acute hepatic failure
- Aplastic anemia
- Autoimmune hemolytic anemia
  - Warm
- Cardiomyopathy, dilated
  - New York Heart Association class II to IV
- Antibody mediated Heart transplant rejection
- Hemochromatosis, hereditary
- Multiple myeloma with polyneuropathy
- Multiple sclerosis (progressive)
- Paraneoplastic neurologic syndromes
- Post-transfusion purpura
- Progressive systemic sclerosis
- Thyroid storm
Finally, the American Society for Apheresis currently has determined that the role of therapeutic plasma exchange is either ineffective or may cause harm in the following conditions.¹²

- Systemic amyloidosis
- Amyotrophic lateral sclerosis
- Burn shock resuscitation
- Coagulation factor inhibitors
- Dermatomyositis or polymyositis
- Hemolytic-uremic syndrome
  - Typical
  - Diarrhea associated
- Immune thrombocytopenic purpura
- Inclusion-body myositis
- Pemphigus vulgaris
- POEMS (Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome
- Psoriasis
- Rheumatoid arthritis
- Stiff-person syndrome

For all these conditions, the specifics of the plasma exchange must be individualized. These can include the frequency of the procedure, the volume to be exchanged at each procedure and the replacement fluid to be used (i.e., 5% albumin versus fresh frozen plasma).

More recently, special filters have been included that can remove specific blood proteins such as Low Density Lipoprotein (LDL), other apolipoprotein
B100-containing lipoproteins or specific immune proteins (immunoadsorption procedures).\(^{79-81}\)

**Cytapheresis**

Cytapheresis is the removal of *cells* from blood; the plasma and the non-selected cells are then re-infused into the donor. The most common use for cytapheresis is erythrocytapheresis, where damaged or defective RBCs are removed and normal RBCs are substituted. Erythrocytapheresis is commonly used in sickle cell anemia (SCA) patients with acute chest syndrome, stroke or frequent and/or severe sickle cell crises. It can also be used in pregnant patients with SCA. Additionally, the hepatitis B surface (HBs) levels can be decreased to less than 35% of pre-treatment levels without risking the increased viscosity (due to an increased hematocrit) that can occur using packed RBC.\(^{82-84}\)

In acute and chronic leukemias, cytapheresis, specifically leukocytapheresis, has been used, treating leukostasis (severe leukocytosis) and concomitant splenomegaly. The reduction in leukocyte burden is temporary, but has been recommended as therapeutically useful.\(^{85,86}\) Platelets are not replaced as quickly as white blood cells and thrombocytapheresis (platelet-specific cytapheresis) has been effective in patients with thrombocytosis (thrombocythemia) and myeloproliferative disorders.\(^{87-89}\)

Cytapheresis may also be used to harvest autologous or allogeneic peripheral stem cells as a potential alternative to bone marrow
transplantation procedures.\textsuperscript{90} Finally, cytapheresis is being investigated to collect and purify antigen-specific lymphocytes for use in adoptive immunotherapy.\textsuperscript{91,92}

Photopheresis is a specialized procedure where lymphocytes are treated with a photosensitizing agent such as 8-methoxypsoralen. On irradiation with ultraviolet light (UV light), the lymphocytes become activated. They are then re-infused into the body to treat a number of conditions, including graft versus host disease (GVHD) and transplant rejections.\textsuperscript{81,93,94}

The American Society for Apheresis currently recommends cytapheresis as 1\textsuperscript{st} line therapy for:\textsuperscript{12}

- Severe babesiosis
  - RBC exchange
- Cutaneous T-cell lymphoma
  - Erythrodermic
  - Photopheresis
- Familial hypercholesterolemia
  - Homozygous
  - Lipid absorption
- Heart transplant rejection
  - Prophylactic
  - Photopheresis
- Hyperleukocytosis with leukostasis syndrome
  - Leukodepletion or Leukoreduction
- Sickle cell disease with acute stroke
  - RBC exchange
The American Society for Apheresis currently recommends cytapheresis as 2\textsuperscript{nd} line therapy, either alone or in combination with other treatment(s) for:\textsuperscript{12}

- Cryoglobulinemia due to hepatitis C
  - Immune-adsorption
- Familial hypercholesterolemia
  - Heterozygous
  - Lipid absorption
- Graft versus host disease
  - Skin involvement
  - Photopheresis
- Heart or lung transplant rejection
  - Treatment
  - Photopheresis
- Inflammatory bowel disease
  - Adsorptive cytapheresis
- Malaria, severe
  - RBC exchange
- Rheumatoid arthritis
  - Refractory
  - Immune-adsorption
- Sickle cell disease with acute chest syndrome
  - RBC exchange
- Thrombocytosis, symptomatic
  - Platelet depletion

The American Society for Apheresis currently has determined that the role of therapeutic plasma exchange has not yet been defined and any decision to
treat with cytapheresis should be made on an individual basis. In addition, Institutional Review Board (IRB) approval should be obtained.\textsuperscript{12}

- Coagulation factor inhibitors
  - Immune-adsorption
- Cutaneous T-cell lymphoma, non-erythrodermic
  - Leukodepletion
- Graft versus host disease
  - Systemic or non-skin involvement
  - Photopheresis

- Pemphigus vulgaris
  - Photopheresis
- Polycythemia vera or erythrocytosis
  - RBC depletion

Finally, the American Society for Apheresis currently has determined that the role of therapeutic plasma exchange is either ineffective or may cause harm in the following conditions.\textsuperscript{12}

- Dermatomyositis or polymyositis
  - Leukocytapheresis may be ineffective or cause harm
- Inclusion-body myositis
  - Leukocytapheresis may be ineffective or cause harm

**Intrauterine Fetal Blood Transfusion:**

**Rh Disease (Erythroblastosis Fetalis)**
Rh\textsubscript{D} negative mothers carrying a Rh\textsubscript{D} positive fetus are at risk of sensitization to the Rh\textsubscript{D} antigen. In a sensitized mother carrying an Rh\textsubscript{D} positive fetus, the fetus is at risk for Rh disease or erythroblastosis fetalis, also known as hemolytic disease of the newborn.\textsuperscript{95,96}

**Rh Blood Group System**

The Rh (for the Rhesus monkey in which it was first described) system is one of the more clinically important blood group systems. There are over 50 known Rh antigens. The “D” antigen is coded for by a region on chromosome 1 and appears to code for a RBC membrane transport protein. The inheritance of the D antigen can be best understood as a single dominant gene with a positive (D) and negative (d) allele. In other words, an individual either has the allele or is therefore Rh\textsubscript{D+} or, the individual does not, and he or she is Rh\textsubscript{D-}.

In the table below, the **red shading** indicates Rh\textsubscript{D+} and **yellow shading** indicates Rh\textsubscript{D—}.

**Table 10**

<table>
<thead>
<tr>
<th>If Mother is →</th>
<th>DD</th>
<th>Dd</th>
<th>Dd</th>
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</thead>
<tbody>
<tr>
<td>If Father is ↓</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>DD</td>
<td>DD or Dd</td>
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<tr>
<td>Dd</td>
<td>DD or Dd</td>
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<td>Dd</td>
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<tr>
<td>dd</td>
<td></td>
<td></td>
<td>Dd</td>
</tr>
</tbody>
</table>

\[85\]

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Expectant mothers are screened for potential Rh\textsubscript{D} incompatibility between the mother (Rh\textsubscript{D}-) and the fetus (Rh\textsubscript{D}+). At 28 weeks of gestation the mothers are given an injection like RhoGam\textsuperscript{TM} or MICROhoGam\textsuperscript{TM}, which contains human anti-D IgG-class antibody. IgG can cross the placenta and can suppress the immune response to the Rh\textsubscript{D} antigen. The injection is also given post-partum to protect against a response to any Rh\textsubscript{D}+ fetal cells that leaked into the maternal circulation during birth. This treatment prevents the majority of cases of Rh disease (erythroblastosis fetalis, hemolytic disease of the newborn).

Signs of Rh disease in the fetus include hepatomegaly, splenomegaly and cardiomegaly. Abdominal ascites in the fetus is also a symptom of Rh disease. The older term for ascites and edema in the fetus is fetal hydrops. Signs and symptoms of Rh disease in the newborn are:

- Hemolytic anemia
- Jaundice
- Hepatomegaly
- Splenomegaly
- Edema
- Ascites
- Dyspnea

If Rh disease is detected in the fetus, an intrauterine fetal blood transfusion may be performed. This involves the guided introduction of a compatible blood type (usually O-) via a needle into the fetal umbilical cord vein or the fetal abdomen.

There is no universally recognized protocols for performing an intrauterine blood transfusion, though there have been a number of studies indicating
that overall survival of the infant after an intrauterine transfusion exceeds 90%. A recent Cochrane review concluded that more studies are needed.

Complications Involved In Blood Transfusions: Part II

There are three main categories of risk in blood transfusions:

1. Immune reactions
2. Non-immune reactions
3. Infections

These reactions may be immediate or delayed by 2 - 14 days.

Immediate Reactions

Immune reactions may be immediate. These include the following conditions.

- Direct allergic reactions characterized by urticaria (hives), itching along with respiratory symptoms such as wheezing or stridor in severe cases may occur. The incidence is 1-3%.  

- Febrile, non-hemolytic transfusion reactions are induced by an immune response to antigens present on the white blood cells or platelets. These reactions are characterized by an increase in body temperature of greater than 1°C above baseline (pre-transfusion). Chills or rigors may accompany the febrile response, and is most frequently seen within 2 hours post-transfusion. The incidence is 0.1-1%.  

[87]
• Frank hemolysis usually due to a mismatch of blood or blood components. Incidence is 1/6000 and is commonly caused by human error at the bedside such as mis-labeling or mis-reading a label or patient mis-identification, but may be caused by errors in crossmatching and/or typing. Ranges from 1 in 40,000 to 1 in 76,000 depending on whether the reaction is due to histoincompatibility or to pre-formed antibodies respectively. It may be fatal (incidence 1 in 1.8 million). 

• Transfusion-Related Acute Lung Injury (TRALI) is another immune reaction that can occur. The pathologic mechanisms underlying TRALI are not well understood, but are believed to be due to either alloreactive leukocyte (human leukocyte antigen [HLA] or human nuclear antigen [HNA]) antibodies. However, there are a significant number of cases where TRALI has occurred in the absence of any detectable anti-HLA or anti-HNA antibodies. Risk of TRALI may be associated with the use of buffy-coat (WBC)-derived platelets that have been stored for longer periods of time, but tests of such samples have not revealed any significant levels of antigens nor have these samples been shown to increase the risk of TRALI.

TRALI occurs within 6 hours of transfusion in patients with no pre-existing lung conditions and is characterized by pulmonary edema and hypoxia. The incidence is 1/10,000.
• **Transfusion Associated Circulatory Overload (TACO)** results from fluid overload that overwhelms the patient’s capacity to handle the volume. TACO was the second most reported adverse fatal event relating to transfusions (TRALI was associated with the most common cause of death). In fact, the incidence of TACO is increasing, and may be under-reported, while the incidence of TRALI is decreasing. In a recent study of TACO, 6% of patients in the intensive care unit (ICU) were diagnosed and the risk factors included positive fluid balance, larger volume of transfusion, greater plasma transfusion volume, and a faster transfusion rate.

• Anaphylaxis occurs in 1/20,000 to 1/50,000 patients and is due to immediate type hypersensitivity responses. For example, it can occur in IgA-deficient patients with pre-existing anti-IgA antibodies that react with IgA in the donor plasma. The response results in mast cell degranulation in tissues. Symptoms include hypotension (low blood pressure), urticaria (hives), bronchospasm (asthma attacks), angioedema (hive-like lesions under the skin) and anxiety.

Non-immune reactions may occur as well, such as, volume overload. Volume overload is most commonly due to a too-rapid transfusion, especially in patients who have limited cardiovascular reserve. The major risk factors for volume overload are age (the elderly and infants) and either pre-existing cardiovascular or renal disease.

**Delayed Reactions**
Delayed transfusion reactions tend to be immune-based. Some delayed hemolytic reactions appear to be anamnestic or secondary memory immune responses to past pregnancies or a previous transfusion history. Hemolysis and jaundice appear several days after transfusion. Other delayed hemolytic reactions appear to be due to mechanical disruption of the RBCs that may be due to centrifugation problems, temperature changes or the use of non-isotonic fluids.

Post-transfusion purpura appears usually 2 - 14 days post-transfusion with a purpuric rash, bruising and/or bleeding from mucosal surfaces. Lab results indicate an associated thrombocytopenia, sometimes severe.

Transfusion-associated graft-versus-host disease is where the donor lymphocytes (the graft) recognize and attack the recipient tissues.

Infections are considerably more rare since donors are screened and pre-tested and sterile methods are in place both in the blood bank and at the bedside. Most blood banks also employ a number of bacteriological and viral surveillance measures on blood products. The main infectious risks and incidences are listed in the table below.⁹

### Known Risk Factors For Transfusion Reactions

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1</td>
<td>1 in 1,467,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 in</td>
</tr>
</tbody>
</table>

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There are no known risk factors for allergic reactions, but the risk of anaphylactic reactions may be increased in IgA deficient patients.¹⁰⁰

There are some known risk factors for TRALI. These include:

- A history of chronic alcohol abuse
- Sepsis
- Female donors, especially those with a higher number of pregnancies.
- Donor units that test positive for anti-granulocyte antibodies and anti-HLA class II antibodies.
- The level of lysophosphatidylcholine in the transfused blood component.

Risk factors for volume overload include:

- Age
  - The elderly and infants are at higher risk
- Patients with pre-existing cardiovascular disease
- Patients with pre-existing renal disease

Risk factors for GVHD include:

- An immunocompromised host
- The donor is a related (biological) family member

<table>
<thead>
<tr>
<th>Table 11: Risks of Infections in Transfusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B</strong></td>
</tr>
<tr>
<td>1 in 282,000</td>
</tr>
<tr>
<td><strong>West Nile Virus</strong></td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Cytomegalovirus</strong></td>
</tr>
<tr>
<td>Leukocyte reduction is protective, but 50 - 85% of donors are carriers.</td>
</tr>
<tr>
<td><strong>Bacterial Infection</strong></td>
</tr>
<tr>
<td>1 in 2 - 3,000</td>
</tr>
<tr>
<td>(mostly platelets)</td>
</tr>
<tr>
<td><strong>Parasitic Diseases such as Babesiosis, Chaga’s, Malaria</strong></td>
</tr>
<tr>
<td>Relatively uncommon</td>
</tr>
</tbody>
</table>
• Donor has a human leukocyte antigen (HLA) homozygous haplotype which is identical with the patient’s HLA haplotype
• Recipient is recognized as foreign by donor lymphocytes and the graft/donor lymphocytes. The skin, liver, immune system, and bone marrow are preferentially attacked by the donor lymphocytes.

Risk factors for post-transfusion purpura include:
• Women who have been pregnant
• History of transfusion and sensitization to the platelet antigen, HPA-1a.

**Transfusion-Related Acute Lung Injury (TRALI)**

Transfusion-Related Acute Lung Injury (TRALI) is the most common cause of transfusion-related deaths in the U.S.\(^{101}\) TRALI is an acute lung injury, defined as “acute hypoxemia with a Pa\(_{O2}\)/Fi\(_{O2}\) ratio of less than or equal to 300 mm Hg with bilateral pulmonary edema on frontal chest radiograph and either pulmonary artery occlusion pressure less than or equal to 18 mm Hg or no clinical evidence of left atrial hypertension.”\(^{102}\) Some of the risk factors associated with acute lung injury include severe sepsis, pneumonia, aspiration of gastric contents, drug overdose, burns, disseminated intravascular coagulation, near drowning, shock, cardiopulmonary bypass, and massive transfusions.\(^{103}\)

The National Heart, Lung and Blood Institute (NHLBI) defines TRALI as “new onset acute lung injury (ALI) with onset of symptoms within 6 hours of transfusion with no preexisting ALI before the transfusion and confirmation through assessment of the patient’s clinical course.”\(^{104}\) TRALI is primarily a diagnosis of exclusion, and since it often has a delayed appearance, it is
important that the nursing staff and other health professionals maintain their awareness of and vigilance for the occurrence of TRALI. There is currently no lab test that is diagnostic for TRALI.

Transfusion related acute lung injury is most commonly associated with the transfusion of plasma-containing products, usually fresh frozen plasma. Symptoms include dyspnea, fever (1°–2° C increase), hypotension, tachycardia (rapid heart rate), tachypnea (rapid respiratory rate), frothy endotracheal aspirate, cyanosis (bluish lips, skin), and severe hypoxemia (lack of oxygen). If there are no symptoms of heart disease or dysfunction or signs of acute volume overload, TRALI should be considered and a chest X-ray should be ordered. X-rays may show a “whiteout” appearance similar to acute respiratory distress syndromes (ARDS). Transfusion-associated circulatory overload (TACO), bacterial contamination, and anaphylactic transfusion reactions need to be ruled out as well.

The most common association with TRALI is the presence of antibodies against the human leukocyte antigen (HLA) system. The HLA system describes the major histocompatibility complex (MHC) for humans and functions in infectious diseases, graft rejection, autoimmunity and in cancer surveillance and metastasis. The genes for the human MHC complex are found on chromosome 6 and encode cell-surface antigen-presenting proteins (found on antigen-presenting cells (APC) like macrophages and dendritic

[93]
cells). HLA antigens may be Class I (those that are found on APCs) or Class II, which play a role in the production of antibodies and autoantibodies by B cells. Women who have had one or more pregnancies often have detectable anti-HLA antibodies in their sera or plasma.

The proposed mechanism of TRALI involves HLA antibodies that are present in donor plasma. These antibodies are presumed to react with the patient’s (recipient’s) immune system, specifically affecting the pulmonary vasculature and increasing permeability. The increased permeability allows for the entrance of polymorphonuclear neutrophils [PMN] into the lung. PMN activation then can result in endothelial damage, capillary leakage, and eventually, massive bilateral pulmonary edema, as seen in TRALI. There have also been a number of reports of the association of TRALI with antibodies to human neutrophil antigens (HNAs). For example, HNA-3a is present in ~ 95% of humans and antibodies to HNA-3a can activate neutrophils. In animal models of TRALI, these activated neutrophils damage the pulmonary microvasculature in ways that strongly resemble those seen in TRALI. Lab results sometimes show a transient decrease in peripheral WBC, which, if noted, can be a useful sign. The storage time of blood products may also be a concern with TRALI, with longer storage of buffy-coat associated platelets linked to an increased risk of TRALI.

Supportive treatment should occur as soon as TRALI is suspected. The transfusion should be stopped immediately and the blood bank should be notified right away. Supportive treatment constitutes respiratory support and maintenance of hemodynamic status. Donor blood should be tested for HLA and HNA antibodies. If these are negative, the donor blood should be tested for WBC antibodies. If any antibodies are found in the donor samples, the donor should be notified and advised that they should not donate any
plasma or blood components that contain plasma. The patient, once recovered, should be counseled regarding avoiding unnecessary transfusions in the future, even though the likelihood of a second TRALI episode is extremely rare.

In the United Kingdom, as part of the Serious Hazards of Transfusion or SHOT study, using plasma preferentially from male donors was instituted on the basis of the rationale that pregnancy can induce the formation of anti-HLA and anti-HNA antibodies and that males were less likely to produce these types of antibodies. The number of cases of TRALI did drop as did the mortality rate. The American Red Cross has also reported that in the majority of fatalities due to TRALI, the recipient received plasma products from female donors with WBC antibodies. The American Red Cross is currently in the implementation phase of diverting donated female plasma to alternative uses such as protein fractionation and preferentially using male plasma for transfusions.

**Transfusion Associated Circulatory Overload (TACO)**

Transfusion Associated Circulatory Overload (TACO) results from the inability of the patient to compensate adequately for the volume of blood or blood components transfused. This may occur if the patient has an impairment of cardiac function or if the transfusion occurs too rapidly. According to the FDA, TACO is the second most frequent cause of mortality post-transfusion.

Transfusion Associated Circulatory Overload is a relatively common transfusion reaction, occurring most often in the elderly or the very young.
As little as 1-2 units may induce TACO, causing a cardiogenic pulmonary edema. This can occur during the transfusion or up to 6 hours post-transfusion. Symptoms include those of congestive heart failure:

- Dyspnea and/or orthopnea (dyspnea when lying flat)
- Tachycardia
- Hypertension
- Increased venous pressure (increased distention of the jugular vein may be noted)

Pulmonary auscultation may reveal lung crackles and/or rales and an elevated jugular venous pressure (JVP). Chest X-ray may reveal alveolar and interstitial edema, distended pulmonary artery and cardiomegaly (an enlarged heart). Lab studies indicate that brain natriuretic peptide (BNP) is 81% sensitive and 89% specific for TACO.\textsuperscript{58,117} BNP, also known as ventricular natriuretic peptide, is secreted by cardiomyocytes in the ventricles as a response to distention. Ca\textsuperscript{2+} levels are important in regulating the release of BNP. BNP functions to increase the excretion of sodium and to decrease vascular resistance, resulting in a decrease in blood pressure.

If TACO is suspected and the transfusion is still being administered, the transfusion should be stopped immediately and the blood bank should be notified. Standard treatment is with diuretics and respiratory support measures. Ultrafiltration is currently being investigated to replace diuresis.\textsuperscript{119}

\textbf{Acute Kidney Injury (AKI)}
The phrase “Acute kidney failure” (ARF) has been replaced with more commonly used phrase Acute Kidney Injury (AKI). AKI is the abrupt decrease in kidney function that may be partial or complete. The net result is the retention of waste products. In transfusion patients, AKI is caused by high levels of hemoglobin (hemoglobinuria) induced by the widespread hemolysis of the RBC.

The diagnostic criteria for acute kidney failure are the presence of any of the following:

- An increase in serum creatinine level of 0.5 mg/dL
- A 50% increase in creatinine level above baseline value
- A 50% decrease in baseline glomerular filtration rate (GFR)
- Oliguria, which is defined as urine output less than 400 mL/24 hours
- Anuria, which defined as urine output less than 100 mL/24 hours

Rifle and AKIN Criteria for Acute Kidney Injury

RIFLE System

The RIFLE classification for acute kidney injury in critical care was developed after a systematic review and an expert consensus conference.\textsuperscript{120,121} The classification is divided into categories of Risk, Injury, Failure, Loss of function and End-stage kidney disease. The risk, injury and failure categories are based on the glomerular filtrations rates (GFR) and urine outputs.

Risk of renal dysfunction:

- GFR criteria
• Increased serum creatinine 1.5-fold, or
• GFR decrease by greater than 25%

• Urine output criteria
  o Urine output of less than 0.5 mL/kg/hour for 6 hours

Injury to kidney:
• GFR criteria
  o Increased serum creatinine 2-fold, or
  o GFR decrease by greater than 50%
• Urine output criteria - urine output of less than 0.5 mL/kg/hour for 12 hours

Failure of kidney function:
• GFR criteria
  o Increased serum creatinine 3-fold, or
  o GFR decrease of greater than 75%, or
  o Serum creatinine of greater 4 mg/dL in a setting of an acute increase of at least 0.5 mg/dL
• Urine output criteria
  o Urine output of less than 0.3 mL/kg/hour for 24 hours (oliguria), or
  o Anuria for 12 hours

Loss of kidney function (persistent AKI) is defined as the complete loss of kidney function for more than four weeks.

End Stage Kidney/Renal Disease (ESK/RD)
End stage kidney or renal disease is defined as the complete loss of kidney function for more than three months.

**AKIN System**

The Acute Kidney Injury Network (AKIN) also has proposed diagnostic and classification criteria. These two systems have obvious similarities, but also have some important differences—a third classification system, the **Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines** attempts to reconcile the two systems. (See below).

**Diagnostic Criteria:**

One of the following is required with a 48-hour period:

- An absolute increase in serum creatinine of greater than or equal to 0.3 mg/dL percentage increase in serum creatinine of greater than or equal to 50% (1.5-fold from baseline)
- A reduction in urine output with documented oliguria of less than 0.5 mL/kg/hour for more than 6 hours

**Classification system:**

- **Stage 1**
  - **Serum creatinine criteria**
    - An increase of greater than or equal to 0.3 mg/dL, or
    - An increase to 150% - 200% from baseline
  - **Urine output criteria**
    - Less than 0.5 mL/kg/hour for more than 6 hours
- **Stage 2**
  - **Serum creatinine criteria**
    - An increase to 201%-300% from baseline
Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines

As mentioned, there are differences between the RIFLE and the AKIN systems. The Kidney Disease Improving Global Outcomes (KDIGO) system is an effort to reconcile the two systems.124-126

Staging:

- **Stage 1**: With any one of the following -
  - Serum creatinine 1.5 - 1.9 times baseline
  - Serum creatinine \textit{greater than or equal to} a 0.3 mg/dL increase.
  - Urine output of \textit{less than} 0.3 mL/kg/hour for 24 hours, or
  - Anuria for 12 hours

- **Stage 2**: With either of the following -
  - Serum creatinine 2 - 2.9 times baseline
  - Urine output of \textit{less than} 0.5 mL/kg/hour for 12 hours or more

- **Stage 3**: With any one of the following -
  - Serum creatinine \textit{\geq} 3 times baseline
- Increase in serum creatinine to \textit{greater than or equal to} 4 mg/dL
  - This criteria holds \textit{after} the definition of acute kidney injury is met
  - An increase in serum creatinine by \textit{greater than or equal to} 0.3 mg/dL within 48 hours or an increase of \textit{greater than or equal to} 1.5 times baseline.
- Initiation of renal replacement therapy
- Anuria for 12 hours or more
- Urine output of \textit{less than} 0.3 mL/kg/hour for 24 hours or more
  - In patients less than 18 years old, a decrease in estimate glomerular filtration rate (eGFR) to less than 35 mL/minute per 1.73 m$^2$

\textbf{Disseminated Intravascular Coagulation (DIC)}

Disseminated Intravascular Coagulation (DIC) complicates many illnesses and is a rare but significant complication of transfusion procedures. It is also known variously as consumptive coagulopathy, defibrination syndrome and defibrinogenation syndrome. DIC is characterized by the systemic activation of the regulatory and functional coagulation pathways and results in the generation of fibrin clots (causing organ failure due to the resultant ischemia) and the consumption of platelets and coagulation factors that may promote bleeding — a particularly significant problem in transfusion patients.

There are two forms of DIC:

\begin{itemize}
  \item Note: If urine output and serum creatinine lead to different stages, patient should be assigned the \textbf{higher} stage.
\end{itemize}
• Fulminant or overt:
  This is the acute form of DIC resulting from a decompensated
  hemostatic system. Overt DIC may be controlled or uncontrolled.
  o Controlled:
    Controlled DIC represents “temporary override” of the regulatory
    network of the endothelium. An example would be the activation
    of Protein C by thrombomodulin. Controlled DIC reverses rapidly
    when the predisposing factor is removed. In transfusion
    reactions, this translates to the immediate cessation of the
    transfusion.
  o Uncontrolled:
    Uncontrolled DIC represents the degradation of the endothelial
    regulatory network in addition to an override of the network.
    The degradation of the regulatory network can be in response to
    trauma or sepsis and can therefore occur in patients undergoing
    emergency transfusion for acute injury. Uncontrolled DIC may
    not cease when the transfusion process is halted and the clinical
    decision must often be made to continue the transfusion and to
    add, for example, cryoprecipitate (containing concentrated
    coagulation factors) and/or platelet rich plasma (PRP) in an
    attempt to replace the consumed coagulation factors and
    platelets.
• Non-overt or “low grade” DIC:
  This is the chronic form of DIC resulting from a stressed but still
  functional and compensating hemostatic system.

Many of the understood and presumed pathogenic mechanisms of DIC can
occur pre-transfusion, i.e., traumatic tissue damage or RBC damage, during
the circulation or deposition of immune complexes (IC) composed of antigen bound to specific antibody or endotoxin release; and, post-transfusion, *i.e.*, IC deposition causing endothelial damage, RBC damage, endotoxemia, tissue damage or platelet damage.

Regardless of the specific pathogenesis, the resulting process is the same with, sometimes, massive activation of plasmin and thrombin by both the intrinsic and extrinsic coagulation pathways (see above) with resultant vasodilation, loss of endothelial tight junctions leading to leakage and possible shock. Additionally, the consumption of platelets and coagulation factors can worsen the anemia, bleeding and cause additional hemorrhage into tissues. Besides the activation of the coagulation pathways, the normal, physiologic anticoagulant pathways are simultaneously suppressed because anti-thrombin levels are reduced by the increased utilization of antithrombin, increased enzymatic degradation, impaired neosynthesis by the liver and by leakage into extravascular spaces, due in part to the leakage across the weakened tight junctions, the vasodilation and common compensatory increase in blood pressure as the body strives to maintain blood flow.\textsuperscript{127-130}

\textbf{Massive Transfusions}

The most recent studies, sometimes based on research and data accumulated in combat hospitals, involve the ideal ratio of units of packed RBC to units of plasma or platelets that can increase survival and decrease the nature and the degree of complications.\textsuperscript{10,127,131-135} Current data indicates that early transfusion of units of plasma, platelets and coagulation factors while at the same time transfusing packed RBCs can decrease both mortality and morbidity.\textsuperscript{10,131-135} This, in fact, runs counter to many of the
official guidelines which do not recommend using crystalloid or colloidal fluids (i.e., FFP, PRP, cryoprecipitates) in conjunction with the use of packed RBC’s or whole blood.\textsuperscript{11,136-139}

**RBC Transfusion and Sepsis**

Sepsis is the systemic inflammatory response to infection and affects pediatric, neonatal and adult critical care. Many of the critically ill patients who are thought to require and are transfused with packed RBC or blood components are septic. A small number of those who receive packed RBC or blood components will become septic. The greatest risk of bacterial infection is after the transfusion of platelets. (See Table 11, above).

It has become increasingly accepted in the medical community that RBC transfusion can lead to great morbidity and mortality, particularly when transfused with older RBC.\textsuperscript{140-144} So, those septic patients who require RBC transfusions must be monitored closely. In addition, those patients who become septic after platelet or other blood component transfusion must also be monitored closely.

Sepsis is an inflammatory response and stimulates and activates both the innate and acquired immune systems. Inflammatory pathways are activated and various cytokines and inflammatory mediators are secreted causing a number of potentially detrimental effects including vasodilation, increased capillary permeability, increased expression of adhesion molecules and an activation of the clotting pathways evidenced by increased clot formation and decreased clot dissolution (fibrinolysis). All these events can lead to serious hypotension and multiple organ failures.\textsuperscript{142,143,145,146}
As with any transfusion reaction, the prompt identification, recognition and treatment of sepsis are critical. In addition, the recognition that the addition of RBC to the treatment of septic patients may have adverse effects on the outcomes, must be recognized as part of the responsibilities of the nursing staff and part of what the nursing staff must be aware of as they monitor their septic patients after transfusion and as they monitor their transfusion patients for sepsis.

The “Surviving Sepsis Campaign”\textsuperscript{143,147} provides guidelines for nursing staff in “bundles”. The benefits of routine screening of patients at risk for sepsis is emphasized and acknowledges that care of the septic patient necessitates a multidisciplinary team approach and included infection prevention.

**Infection, Prevention and Source Control**

Hand hygiene, catheter care, comprehensive oral care and barrier precautions should be followed. Both selective oral decontamination and selective digestive decontamination approaches should be used to reduce the incidence of ventilator-associated pneumonia.

Every effort should be made to identify the source of infection with appropriate interventions taken as soon as possible. This can include debridement, assessment and subsequent removal of suspicious access devices and tubing and the observation of the patient for striae, tender areas or other signs of inflammation and infection.

*Initial Nursing Response to Sepsis*
Within three hours of the initial diagnosis of sepsis, patients should have lactate levels measured and blood cultures drawn for both aerobic and anaerobic cultures. These must be drawn before the administration of broad spectrum antibiotics. One sample should be obtained through venipuncture and at least one sample should be obtained through each vascular access device. Other samples for culture may be obtained (i.e., respiratory secretions, other body fluids) depending on the individual patient. Sepsis induced hypoperfusion is defined as hypotension that is refractory to the administration of 30 mL/kg crystalloids (albumin) for hypotension or a lactate level of greater than or equal to 36mg/dL (4 mmol/L). If the hypotension is refractory, the guidelines recommend the use of vasopressors (norepinephrine/epinephrine) to maintain mean arterial pressure greater than or equal to 65 mm Hg.

Additional targets include a central venous pressure of at least 8 mm Hg, and central venous O₂ saturation of at least 70 %. Urine output should be at least 0.5 mL/kg per hour. It should be noted that the use of steroids is no longer universally recommended and studies have failed to show any benefit for steroid use except potentially in those patients who are hemodynamically unstable after both fluid challenge and administration of a vasopressor.

Setting the goals for care and discussing these goals with the patient and patient’s family are high priorities with the Surviving Sepsis Campaign guidelines. These discussions should occur within 72 hours of admission to the ICU and should include discussions about palliative care and end-of-life care.
Transfusion-Associated Graft-Versus-Host-Disease

The use of irradiated blood products and reduction in the number of donor WBCs transfused (leukoreduction) is the current standard of care to prevent transfusion-associated graft-versus-host disease (TA-GVHD) that has a greater than 90% mortality rate. The initial stages of GVHD may be confused with allergic reactions. It is vital to differentiate between allergic reactions and TA-GVHD because the combined effects of the donor immune cell response to the recipient's tissues and the resulting bone marrow aplasia and neutropenia place the recipient at a very high risk of sepsis.149

As mentioned in the section on infections, donors and recipients are tested and screened for a very small fraction of the number of potential pathogens. Because of this, and to even further reduce the risk of TA-GVHD, recent research has focused on pathogen reduction protocols.149 A number of these protocols are used in Europe and it is possible that some or most of these approaches may be adopted in the U.S. The protocols include the use of combinations of agents along with ultraviolet (UV) light, visible light or detergents to kill pathogens and decrease the proliferations of immune lymphocytes.149

Graft versus host disease is a significant concern in allogeneic stem cell transplants to treat hematological cancers. Current and experimental approaches to the treatment of TA-GVHD include supportive care, mesenchymal stem cell salvage techniques, the use of short-term immunosuppressive agents and monoclonal antibodies against antigens expressed on T and B cells.149-154
Hypotension: ACE Inhibitors

Acute hypotension after transfusion appears to be related to the use of angiotensin-converting enzyme (ACE) inhibitors because of the role that ACE plays in bradykinin metabolism. Bradykinin is a vasodilatory peptide whose level is increased in patients taking ACE inhibitors to lower blood pressure. These hypotensive reactions have also been associated with the use of bedside leukocyte-reduction filtered blood products.\textsuperscript{155-157}

Step-by-Step Procedure For A Suspected Transfusion Reaction

These steps have been derived by the AABB and follow generally accepted guidelines. Nursing staff must know, in addition, the specific policies and protocols for their individual hospital and institution and follow those as required when a transfusion reaction is suspected.

1. \textit{STOP} the transfusion \textit{IMMEDIATELY}

2. \textit{Disconnect the IV line FROM THE NEEDLE.}
   a. Do NOT disconnect the (blood component) unit from the IV set.
   b. Attach a new IV set
   c. Prime the new IV set with saline
   d. Reconnect and open the line with a slow drip.

3. \textit{Notify the medical staff (physician on duty, the patient’s physician, physician on call, etc.).}
   a. \textit{If necessary, call a code}

4. \textit{CHECK} the patient’s wrist ID and the unit label to ensure that the unit was meant for the patient.
   a. \textit{DO NOT ASSUME ANYTHING. CHECK AND DOUBLE CHECK!!}
5. Do not discard the unit of blood or blood component. The blood bank will need it to determine the underlying cause of the transfusion reaction.

6. Notify the blood bank. Be prepared to briefly summarize and describe the nature of the transfusion reaction you observed.

7. After the blood bank has been notified, begin filling out the Transfusion Reaction Report Form. This may be a paper form or may be an online form, depending on the institution or hospital.

8. If you suspect a hemolytic transfusion reaction, the blood bank will need:

   a. A completed Transfusion Reaction Report
   b. Post-transfusion blood specimens
      i. Obtain a pink-top blood bank tube with EDTA.
      ii. Make certain you invert the sample 8-10x to ensure proper mixing and the prevention of clotting. DO NOT SHAKE.
      iii. You can use a lavender-top tube if a pink-top is not available. Lavender-top tubes also contain EDTA.
      iv. Use the opposite arm to draw specimens (preferably at the opposite antecubital fossa). Hand or wrist veins on the opposite side may also be used.
      v. If it is necessary to draw a specimen from the same IV line that was used for the transfusion (because of collapsed veins, rollers, etc.):
          1. Collect a tube of blood and discard it, as it will be contaminated.
2. Collect and label a pink-top tube as required for testing.

c. The unit(s) of blood or blood components suspected to be causing the transfusion reaction. Clamp the IV tubing used and sent to the blood bank. Do not send the tubing with the needle. Dispose of the needle in the proper container.

d. Be aware that a urine sample may also be requested

9. If the reaction is less severe and non-life threatening, the physician in charge may determine that the benefit of continuing the transfusion outweigh the risk. There may be more specimens requested later.
The algorithm used by the American Society for Clinical Pathology in case of a transfusion reaction is shown below.

Algorithm from the ACP for Transfusion Reactions

General Guidelines For The Transfusion Procedure

Nurses may be considered to be at the frontline of safety for transfusion procedures. It will be up to the nursing staff at the patient’s bedside to be responsible for the proper and accurate identification of the patient and the proper and accurate identification of the blood product, ensuring that the correct patient receives the correct blood component. It is absolutely essential to completely and consistently verify the identity of the patient during every step of the procedure. It is also absolutely essential to verify
that the blood component sent from the blood bank is meant for that specific patient. The general guidelines for performing transfusions of any blood components include:

- Pay attention to identification -
  This includes checking the patient’s wristband with the patient’s chart. Make sure, if possible, that you engage with the patient, asking questions like “Is this how you spell your name”, “I see your first name is Elizabeth. Do you prefer Elizabeth or a nickname like Liz or Beth?”, “Can I double check the spelling of your last name”, “What is your date of birth?” or “Can you verify your date of birth for me?”

- Check blood product label carefully against wristband to ensure that the blood product or blood products is/are intended for that specific patient.
  - Mislabeling of samples, blood, blood products, is a significant but totally avoidable cause of transfusion reactions.

- **ALWAYS** check the expiry date on any blood or blood products to be transfused.

- Blood and blood products must **NEVER** be stored in a medication refrigerator. If for some reason, the blood or blood product is not immediately used, send the blood or blood product back to the blood bank for proper storage.

- Check against the patient’s chart to ensure that whatever blood products were ordered are the same ones that were delivered by the blood bank.

- Ensure that the blood or blood product is not damaged in any obvious or clear way. Check blood for clots or discoloration.
The transfusion should be slow for the first 10-15 minutes. This is meant to protect the patient against any acute reaction that may occur. The signs and symptoms of acute reactions can often be detected during this first phase of the transfusion. Check the hospital or institutional policy for the time frame recommended for this initial phase.

Always monitor the patient before, during and after the transfusion process.

After the initial phase, ensure that the prescribed rate of infusion is appropriate for the patient.

It is strongly recommended that the transfusion ends within 4-6 hours of the removal of the blood or blood components from storage in the blood bank. Check the hospital or institutional policy for the time frame recommended for the transfusion.

Know the hospital or institutional policies on blood tubing. Change the blood tubing according to that policy and discard properly in the appropriate biohazards container when the transfusion is completed.

If a suspected transfusion reaction is observed, stop the transfusion immediately.

Report reactions to the appropriate medical staff, nursing staff, supervisory staff and to the blood bank immediately.

Evidence-Based Medicine Guidelines for the Transfusion Procedure

The following are guidelines derived from the American Association of Blood Banks for nurses and nursing staff. They were developed in accordance with
FDA guidelines and the Agency for Healthcare Research and Quality (AHRQ). The essential recommendations from AHRQ are the following:

- Donated blood is not transfused to the recipient until it has been processed into its separate blood components.
- Red cells are transfused in anemia to provide adequate oxygen delivery.
- Plasma (Octaplas®) is transfused in hemorrhage to provide coagulation factors when the hemorrhage is not caused by the deficiency of a single coagulation factor.
- Platelets (i.e., thrombocytes) are indicated for the management of bleeding or in thrombocytopenia to promote hemostasis when the platelet number or function is insufficient.
- In primary care, the use of blood products is limited to the treatment of symptomatic chronic anemia when no alternative treatment is available.
- Platelet transfusions may also occasionally be administered outside hospital, for example to patients with hematological diseases.

The following are the AHRQ guidelines to the treating physician for blood or blood component transfusion. It is important for nurses to understand the guidelines under which the prescribing physician is functioning.

**Guidelines to the Treating Doctor Regarding Blood Transfusion**

1. A medical practitioner must prescribe a blood transfusion.
   - The prescription must state the type of blood component (red cells, platelets, plasma), the volume to be transfused
and any special requirements (irradiation, washing, phenotyping).

- If necessary, instructions must be given regarding the speed of transfusion, the possible need to warm the product or any other factors to be considered due to, for example, the patient's condition, unless the staff have been issued relevant protocols.

- If the patient has significant cold agglutinins, red blood cell products should be warmed during transfusion using an approved commercial blood warmer.

Note: Emphasis added for Guidelines, which directly impact the transfusion nursing staff.

2. The person carrying out the transfusion must check the prescription and ensure that the red cell packs intended for transfusion have been found by the laboratory compatibility testing to be compatible with the recipient.

- Before a transfusion of red cells, check the result of the compatibility testing and verify that the correct product and patient was used for the test: the donation number on the blood bag label must exactly match the number on the accompanying documentation and they must indicate the compatibility of the unit.

- If the patient has red cell antibodies, ensure that the label on the red cell pack states the absence of the antigens corresponding to the antibodies detected in the patient (the label will state, for example, Jka — indicating the absence of antigen Jka).
3. The blood product must be checked for defects (integrity and cleanliness of the bag; the presence of clots, aggregates, gas or a black-red color of a red blood cell product is suggestive of bacterial contamination; when inspecting platelet concentrates against light the presence of swirling should be observed).

4. Confirmation that the checks have been carried out is done by signing the transfusion form.

5. A blood administration set with an integral 150–200 µm filter, appropriately attached to the pack to be transfused, should be used to transfuse all blood products.

6. Verification of the patient's identity: the patient's identity data must be checked against the data on the blood product.
   - The patient is asked to state his/her identification (ID) details or
   - A person familiar with the patient verifies the identity of the patient (at the bedside); the identification details must also match with the patient's wristband

7. Before starting a transfusion, the patient's vital signs (heart rate, blood pressure, temperature) are checked and recorded. The start time of the transfusion must be recorded. The sticker on the blood product label indicating the unit number should be detached and reattached to the patient notes, or the transfusion is entered in the electronic patient record system.
   - The recording is carried out to fulfill the statutory obligation to ensure the traceability of the blood product from the recipient to the donor and vice versa.

8. If possible, a transfusion is started slowly with a biological pre-check.
• During the first 10 minutes red cells are infused slowly (10–15 drops/min) whilst carefully observing the patient.

9. The same administration set may be used to transfuse several packs of red cells without interruption (according to the capacity of the administration set filter), but it is recommended that the administration set is changed after six hours in order to reduce the risk of bacterial contamination.

• It is recommended that platelets are administered via a separate administration set or they may be transfused first, if transfusion is to continue with red cells. If the tubing has red cells, retention of platelets may occur.

10. Even though transfusion adverse effects often emerge at the beginning of transfusion, the patient must be monitored throughout the entire transfusion.

11. Red cell transfusion should be completed within six hours of removing the pack from the refrigerator to room air. The end time of the transfusion must be recorded.

12. The blood component pack with the administration set is recommended to be stored after transfusion for 24 hours in case adverse reaction investigations need to be carried out.”

**Step-by-Step Guidelines**

**Pre-Transfusion**

Informed Consent:

The nursing staff must ensure that informed consent is obtained from the patient. This is an absolute requirement unless an emergency situation
exists or if the patient is unable to consent and no substitute individual with a legal right to consent is available. If it is at all possible, nurses must also determine that there is no evidence of the patient’s prior wishes to avoid transfusion for either personal or for religious reasons. Informed consent includes allowing the patient, if possible, time to ask questions and time to fully understand the answers. The following position statement from the New York State Nurses Association presents the highest of legal and ethical standards in professional nursing.¹⁵⁹

"The New York State Nurses Association acknowledges that informed consent seeks to establish the rights of the individual through self-determination. Inherent in the employee status of the registered professional nurse are multiple instances of role conflict that arise through the occasionally conflicting responsibilities to the patient, the family, the agency, care-providing colleagues, society, and to the advancement of knowledge. The Nurses Association believes that the registered professional nurse’s role and responsibility in informed consent is to:

- Advocate for the patient’s human rights, including the right to autonomous decision making, assume primacy.
- Advocate that each patient (or their designated health care proxy agent(s)) is given the information necessary for making informed judgments. This information should include, but is not limited to: risks, benefits and alternatives and expected outcomes to any proposed test or treatments.
- Advocate for each patient’s right to freedom from the imposition of another’s beliefs or judgmental attitudes.
- Advocate that the patient or designated healthcare proxy agent(s) have had sufficient communication with the provider providing or performing the treatment and/or procedure.
- Maintain the registered nurses role as a witness to the patient’s signature to the consent.
- Ensure patients are fully involved in planning, implementing and evaluating their personal health care as they are able. If the patient is declared incapacitated, or unable to make decisions about their health care, a designated health care proxy agent should assume the patient’s role in planning, implementing and evaluating care.
- Ensure information received from patients regarding their treatment remains confidential and "such data is used only in ways that are authorized by the patient" (American Nurses Association (ANA), 2008, p. 26) and in compliance with the law.
- Facilitate patients (or their designated healthcare proxy agent(s)) right to determine what will be done with their person. Each patient or health care proxy agent must be permitted to accept, refuse or terminate treatment without duress."
For patients undergoing a transfusion, informed consent implies that they have an understanding of the risks versus the benefits of a transfusion, receive an understandable (by the patient) description of the blood product and that they understand why their physician has ordered a transfusion. Nursing staff must document the informed consent process as well as the questions asked and how they were answered.

The nursing staff also needs to determine if pre-transfusion samples from the patient have been ordered and obtain those as well, always following the guidelines regarding venipuncture and sample acquisition. A pre-transfusion sample may be required for ABO/Rh testing, antibody screening or for a type and crossmatch. Before drawing a blood sample, always check the patient’s arm or wristband ID. Also, remember to engage with the patient as much as possible. The patient may be experiencing anxiety, pain, confusion or any number of other emotions and it is important for their overall wellbeing that they are made to feel as comfortable as possible under the circumstances.

Nurses should review the patient’s chart, review their most recent labs, evaluate and monitor pre-transfusion symptoms. Vitals, including pulse, blood pressure, respiratory rate, temperature and auscultate the heart and lungs.

Only a qualified MD or DO can order a transfusion. The transfusion order must include the following:

- The name of the ordering physician
- The patient’s name and at least one additional unique identifier (i.e., date of birth, admission number, patient ID number, etc.)
- The specific blood component or product
- The amount to be transfused
- The rate of administration
- Any special requirements such as irradiation, additional filtration, pre-warming
- If any pre-medication is required
- The order may include medications for minor allergic reactions (i.e., antihistamines) or for febrile responses (i.e., a non-aspirin antipyretic)

If at all possible, the blood or blood component should be transfused during the daytime hours.

*Obtaining Components from the Blood Bank*

When blood is obtained from the blood bank, the nursing staff should check to ensure that the container is properly labeled with the correct patient name along with a unique identifier. The nursing staff is also responsible for making certain that the type of blood component delivered (i.e., packed RBC, cryoprecipitate, fresh frozen plasma) is the one that has been ordered for the patient. They should also make certain that an adequate amount of the blood product has been delivered.

---

**Principles for an Accurate Blood Draw**

- Take sample **labels** to the patient’s bedside
- Verify that the labels match **both** the wrist band/ID AND the paperwork and chart IDs.
- Label at the bedside **AFTER** the blood draw
- Document that you drew blood—and **never** sign for someone else.
Some blood banks may require a diagnosis or an indication is given for each transfusion. Some blood banks may also require that there be a rationale or reason given for pre-warming a blood product or for the irradiation of a blood product. Your hospital or institution may have specific policies regarding these matters and it is the nurse’s responsibility to be aware of these policies and adhere to them. In emergency situations, other policies may be in force and the nursing staff must be aware of these as well.

**Mislabling**

Missing a mislabeled sample or component, whether it is a sample that you have drawn or has been delivered by the blood bank, is completely avoidable. Also, remember that if something is mislabeled, another patient may be harmed as well, especially in a busy hospital. The box outlined in red has rules to follow that can help minimize these sorts of errors.

**Table 12: Blood Components: Storage and Expiration Values**

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Volume</th>
<th>Temperature Storage</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>250-300mL</td>
<td>2-6°C</td>
<td>42 days</td>
</tr>
<tr>
<td>Plasma</td>
<td>250 mL → 100mL</td>
<td>Frozen</td>
<td>1 year. Once thawed, 24 hrs at 2-6°C</td>
</tr>
<tr>
<td>Platelets</td>
<td>~300mL</td>
<td>20-24°C on agitator</td>
<td>5 days</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>5-15mL</td>
<td>Frozen</td>
<td>1 year. Once thawed, 4 hrs, 20-24°C</td>
</tr>
</tbody>
</table>
Preparing the Patient for Transfusion

Determine if there have ever been any problems with past transfusions by checking the patient’s chart and/or by asking the patient if possible. Check also to see if any premedication has been ordered. Check to see if the patient has a history of allergic reactions or is allergic to any known medications.

Table 13: IV Access for Transfusion Patients

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>IV Access: USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC rapid transfusions for adults</td>
<td>16-18 gauge needle</td>
</tr>
<tr>
<td>RBC routine transfusions for adults</td>
<td>20-22 gauge needle</td>
</tr>
<tr>
<td>Other components</td>
<td>Any adequate size</td>
</tr>
</tbody>
</table>
Blood or blood components cannot come into contact with any medications or with either hypotonic or hypertonic solutions. This type of contact can cause clotting, hemolysis and/or blood component contamination.

All blood components must be infused through a filter. Most filters are 170 μ but can range to 260 μ.

Ensure that the IV access site is dedicated. With CVAD in place, medication in solutions may be infused without damaging blood.

Make sure that IV pumps, blood warmers and rapid infusers are suitable for the specific transfusion and will not damage the blood or blood components.

**Blood Tubing**

Blood tubing is fitted with a 170 - 260 micron (μ) filter to catch fibrin debris. In preparation for the transfusion, flush tubing with normal saline (0.9% saline), completely wetting the filter. Blood tubing must be changed at least every 4 units or within the number of hours specified by hospital or
institutional policy. Blood tubing must be changed according to hospital policy to prevent bacterial growth.

Platelets should *not* be transfused though tubing that has been used for RBC. Platelets will adhere to any fibrin caught in the filter.

Immunoglobulin products (IVIg or IVIG) and albumin do not require blood tubing, but most products are not compatible with normal saline. Blood products for IV infusion that are delivered in glass bottles require vented IV tubing. At the end of the transfusion, the tubing should be disconnected from patient.

Before picking up blood, make sure patient is ready by connecting the primed tubing to the patient IV site and verifying consent again. Arrange for pickup from the blood bank, ensuring the appropriate paperwork is delivered to the blood bank. Depending on the hospital or institution policy, the transfusion should be completed within 4 - 6 hour. If the transfusion is delayed for any reason, return the unused blood or blood components to the blood bank immediately.

**Blood or Components: Five Rights of Transfusion**

The following steps support the nurse to ensure the blood or components are correctly and safely administered to the patient.

- Confirm the order and that informed consent has been obtained.

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The 5 Rights of Transfusion

- Right patient
- Right product
- Right amount
- Right rate
- Right time
• Check the blood or blood components for ID numbers and compatibility information.
• Check for the “Right Product”, i.e., that the correct blood component has been delivered.
• Always check at the patient’s bedside.
• Visually check the unit for clots, discoloration, leaks, or punctures in the bag or cracks in the glass.
• Double-check the blood group compatibility with the patient’s chart information.
• Check the patient’s wristband – spell the patient’s name, checking for any potential mislabeling or errors. Check the patient’s date of birth.
• Check for patient’s name and unique identifiers. Match the patient ID to the label attached to the component from the blood bank.
• Check that the blood unit number and group matches that of the patient (or, if in an emergency it is O - blood or AB - plasma).
• If there are any discrepancies, STOP and call the blood bank.

Some hospitals have 2 people independently checking that all the information is correct and the “5 Rights” have been met. Enter the blood bank label into the patient’s chart. Before starting, get vital signs, i.e., temperature, blood pressure, pulse, and respiratory rate. Oxygen saturation is commonly obtained as well. The blood bank label should remain attached throughout the transfusion process. Repeat auscultation for patients who might be at risk for volume overload (elderly, children, those with pre-existing cardiovascular or pulmonary disease).
Starting the Transfusion

Spiking the Blood component

- Separate port cover until port is just exposed
- Position port covers away from opening to prevent contamination
- Hold bag in one hand and exposed tubing spike in other — do not hang from an IV pole
- Insert the blood tubing spike into the port by turning clockwise ¼ turn — do not over-spike.
- To remove the bag, pull gently while turning counterclockwise with ¼ turns.
- Spiking the blood component properly will ensure easy removal as needed.

Transfusion

- For the first 10 - 15 min, depending on local policies, infuse at a slow rate unless an emergency situation exists.
- After this initial 10 - 15 minute phase, reassess the patient.
- Take and record vital signs.
- If there are no reactions, and increase to prescribed rate.
- Monitor
  - Local hospital or institutional policies may require specific intervals for monitoring the patient and the vital signs.
- Observe, monitor and record if there is suspected reaction.
- Repeat with more units as needed.
- If the patient is at risk for volume overload, unstable or with a history of reactions, repeat vital signs more often.
• Ask the patient, if conscious, if they are experiencing:
  o Hives
  o Chills
  o Rigor/Chills
  o Fever
  o Shortness of breath (SOB, dyspnea)
  o Back pain (may be an early indicator of hemolysis)
  o Pain at infusion site
  o If they are experiencing and difference in how they are feeling, or if they are experiencing any anxiety

• Complete the transfusion within the time frames indicated by policy.
• Disconnect tubing when complete.
• Check and document vital signs.
• Repeat vital signs according to hospital policy.
• Do not leave the blood tubing attached to patient — this increases the risk of bacterial contamination.
• Do not re-use any of the blood tubing.
• Assess for any delayed reactions.

The patient should be given a prepared document regarding delayed transfusion reactions. This information should include the signs and symptoms of a delayed reaction as well as information on what to do and who to contact.

Delayed reactions to a transfusion include:
• A delayed hemolytic reaction (usually about 4-8 days post-transfusion)
  o Symptoms may include fever, fatigue, hematuria (red urine), jaundice
• Iron overload (rare unless there is a history of transfusions)
• Graft Versus Host Disease (very rare; 3-4 weeks post-transfusion)
  o Fever, rash, diarrhea and abnormal liver function tests (LFT)
• Sepsis (rare)
  o Hypotension (low blood pressure), fever, chills, nausea and vomiting, respiratory distress, shock

**Required Documentation**

• Copy of blood bank label should be entered into the patient’s chart.
• Date, start and finish times for the transfusion.
• Type and amounts of each component transfused.
• Blood/component unit number(s).
• The names of the persons starting the transfusion, checking and monitoring the patient.
• Document vitals and any assessments made during the transfusion.
• There may be a transfusion form to be turned into the blood bank at some hospitals or institutions.
• Follow up testing may be required for some patients. This may include:
  o CBCs
  o INR
  o PT/PTT
  o Fibrinogen levels

**Acute Transfusion Reactions**

Acute reactions occur usually within 6 hours of the beginning of transfusion. If *any* transfusion reactions are noted, stop the transfusion *immediately* and:
• Maintain IV access
• Check all vital signs
• Re-Verify patient ID
• Re-Verify that the blood or component unit matches the label on the bag or glass from the blood bank
• Notify the patient’s physician and/or the physician on call
• Remain with the patient
• Notify the blood bank
• Treat the patient as ordered by the physician

**Signs and Symptoms of an Acute Transfusion Reaction**

• Fever
• Chills with or without rigor
• Hives, urticaria or angioedema
• Rash
• Pruritis
• Edema or swelling
• Respiratory distress: dyspnea, SOB, wheezing
• Hypotension or hypertension
• Hematuria (Red urine)
• Diffuse bleeding or oozing at the site of the IV or at CVAD site.
  Bleeding from any site, including mucous membranes
• Lumbar pain
• Anxiety
• Pain at IV site
• Nausea and vomiting
• Headache
Table 14: Summary of the Symptoms/Signs of Acute Transfusion Reactions

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever chills rigor</td>
<td>Sepsis, Acute hemolytic transfusion reaction, TRALI, febrile non-hemolytic reaction transfusion reaction</td>
</tr>
<tr>
<td>Urticaria/hives/Pruritis</td>
<td>Anaphylaxis, minor allergic reaction</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>TRALI, TACO, anaphylaxis</td>
</tr>
<tr>
<td>Hypertension</td>
<td>TACO</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Bradykinin mediated hypotension, Sepsis, Acute hemolytic transfusion reaction</td>
</tr>
<tr>
<td>Hematuria/Red urine</td>
<td>Acute hemolytic transfusion reaction</td>
</tr>
<tr>
<td>Pain</td>
<td>Acute hemolytic transfusion reaction → lumbar, iv site TACO → chest</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Acute hemolytic transfusion reaction, Anaphylaxis, Febrile non-hemolytic transfusion reaction</td>
</tr>
</tbody>
</table>

Guidelines for Continuing Transfusion if Reactions Occurs

The nurse caring for a patient with a blood transfusion reaction should follow facility policy; however, the following are generally accepted steps for the nurse to observe.

- Consult with the physician first. The blood bank physician may be called.
- Medicate as ordered.
• Proceed cautiously as ordered with more frequent checks on vital signs.
• Document every vital sign and every observation.
• Report to blood bank may be required
  o Send to blood bank (if required)
    ✓ Blood or component bag with attached tubing for possible
culture, hemolysis check or clerical check
    ✓ Previous completed blood/component bags if available.
    ✓ Transfusion reaction reporting document with symptoms, signs,
pre- and post- vitals, time of onset, blood bank unit number
    ✓ Post-transfusion blood sample may be required for:
      ▪ Repeat typing/ direct antibody test (DAT/Coombs)
      ▪ Hemolysis check
      ▪ Re-crossmatching
    ✓ May also need:
      ▪ Urine samples
      ▪ Chest x-ray (TRALI/TACO)
      ▪ Blood culture (use a different vein/site for venipuncture)
      ▪ Other samples may be needed to rule out TRALI,
anaphylaxis, acute hemolytic transfusion reactions
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Adult Recommended Treatment</th>
<th>Pediatric Recommended Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Hemolytic Reactions</td>
<td>Diuretic therapy:</td>
<td></td>
<td>Observe the patient for shock, DIC, volume overload or any other adverse reactions.</td>
</tr>
<tr>
<td></td>
<td>Treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 40-80 mg Furosemide (Lasix) IV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dose can be repeated once.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note: The absence of a response to the diuretic within 2-3 hours may indicate acute renal failure (ARF).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydration:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hydrate to a urinary output of at least 100 mL/hr until urine is free of hemoglobin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infuse a loading dose of 0.9% sodium chloride OR 5% dextrose in 0.45% sodium chloride.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chart hourly urine output.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Administering intravenous fluid at 100 mL/hour until the urine is free of hemoglobin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note: If urinary output does not increase, any additional</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fluids should be infused with caution.

<table>
<thead>
<tr>
<th>Allergic/Anaphylactic Reactions</th>
<th>Urticaria/Hives</th>
<th>Urticaria/Hives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• If urticaria develops slowly, antihistamines may be given orally.</td>
<td>Pediatric dosing</td>
</tr>
<tr>
<td>Wheezing</td>
<td>• <strong>Aminophylline</strong> (125-250 mg) IV. Administer slowly ~5 minutes.</td>
<td>• For <strong>Benedryl</strong>, 1-2 mg/kg IM</td>
</tr>
<tr>
<td></td>
<td>• <strong>Epinephrine</strong> (0.1-0.5 mg or 0.1-0.5 mL of a 1:1000 solution) subcutaneously (SC).</td>
<td>• <strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>• SC dose may be repeated at 10-15 minute intervals.</td>
<td>• IV for 25-50 mg per average dose.</td>
</tr>
<tr>
<td></td>
<td>• Total SC dose should not exceed 5 mg in a 24-hour period.</td>
<td></td>
</tr>
<tr>
<td>Severe allergic reactions/Anaphylaxis</td>
<td>• <em>i.e.</em>, laryngeal edema or bronchospasm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>Epinephrine</strong> 0.03 mL/M² (0.03 mg/M² of a 1:1000 solution) given SC.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>A single pediatric dose should not exceed 0.3 mg.</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Febrile Transfusion Reactions**

- Treat with non-aspirin containing NSAIDs or other anti-pyretics
- Treat with non-aspirin containing NSAIDs or other anti-pyretics
<table>
<thead>
<tr>
<th><strong>Chills</strong></th>
<th>Consider sedation</th>
<th>Consider sedation</th>
</tr>
</thead>
</table>
| **TRALI**  | No formal treatment approaches are generally accepted. Supportive care including:  
- Intubation and mechanical ventilation with small tidal volumes.  
- O₂ support  
- Occasionally pressor agents may be required but iv fluids are generally sufficient to maintain bp.  
- Diuretics if needed for volume overload  
- Labs: Chest X-ray | No data available. Supportive care. |
| **TACO**   | Supportive care including:  
- Place patient in an upright position  
- O₂ as needed  
- Diuretics as needed  
- Labs: Chest X-ray | No data available. Supportive care. |

**Summary**

The transfusion of blood and blood components continues to be a critical aspect of medical care. As an integral part of the multi-disciplinary team, nurses are at the frontline of transfusion medicine and should be aware of indications, contraindications and potential reactions to transfusions of any type. The guidelines for nursing care are undergoing constant evolution in
order to provide patients and families with up-to-date information and the best evidence-based practices available.

Please take time to help the NURSECE4LESS.COM course planners evaluate nursing knowledge needs met following completion of this course by completing the self-assessment Knowledge Questions after reading the article. Correct Answers, pages 129 - 133.

1. GM is a 32-year-old AA female who is typed with B+ blood. As a donor, GM can MOST SAFELY provide packed RBC for which of the following individuals?
   a. TS, a 21 year old Asian female with AB+ blood
   b. KT, a 56 year old European male with A- blood
   c. PL, a 76 year old white female with AB- blood
   d. MN, a 5-year-old Hispanic male with B+ blood
   
   Answer: D

2. Your patient is an otherwise healthy 46-year-old male with β-thalassemia and is scheduled for a transfusion of packed RBC. You are with him and are explaining some of the risks and benefits of his upcoming transfusion. Which of the following would be true?
   a. He runs a high risk of graft-versus-host disease along with allergic reactions, a fever, a hemolytic reaction and some very rare reactions but that he will be observed and monitored throughout the transfusion.
   b. He runs a high risk of Transfusion-Related Acute Lung Injury (TRALI) or Transfusion Associated Circulatory Overload (TACO) but that he will be observed and monitored throughout the transfusion.

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c. You should counsel him not to get a transfusion, but to get a shot of iron for his iron deficiency anemia.

d. The transfusion should be completed within 4 hours and there are some risks associated with an RBC transfusion, including allergic reactions, a fever, a hemolytic reaction and some very rare reactions but that he will be observed and monitored throughout the transfusion.

Answer: D

3. **Your patient is typed AB — and is scheduled for an infusion of plasma. Which of the following plasma types is most suitable for your patient?**
   a. AB+
   b. O-
   c. A+
   d. B-

   Answer: B

4. **A patient who is thrombocytopenic is scheduled to receive two units of irradiated platelets from which the leukocytes (WBC) have been removed. You spike the unit with a standard infusion set and get ready to connect directly to her right arm. Something makes you stop — what question do you need to ask yourself?**
   a. Don’t I need to use a standard blood filter?
   b. Shouldn’t I use another leukocyte reduction filter just to be sure her chances of GVHD are reduced?
   c. I should probably ask the blood bank if these platelets have been tested for ABO compatibility, shouldn’t I?
d. I wonder if her platelet level is low enough to get two units of platelets?

**Answer: B**

5. **Which of the following statements is **FALSE**?**
   a. All blood components must be infused through a filter.
   b. The first 15 minutes of a transfusion should be at a slow rate to ensure there are no acute reactions to the transfusion.
   c. Nurses can store blood products in the medication refrigerator as long as the temperature is monitored.
   d. If a patient has a history of cold agglutinins, a blood-warming unit may be ordered, but it is not absolutely required.

   **Answer: C**

6. **A transfusion is started at 9:30 am. The packed RBCs were signed out of the blood bank at 8:30 am, but the patient’s IV has blown. It is now 10:30 am and the transfusion is not complete. At what time should the transfusion be stopped, whether or not it is complete?**
   a. By 12:30 pm—4 hours after the blood was signed out.
   b. By the end of the shift—at 11 am.
   c. By 4:30 pm. Blood should be used within 8 hours of signing out of the blood bank.
d. It doesn’t matter because the packed RBCs have been irradiated, so there is little risk of infection.  

**Answer: A**

7. You notice that your patient’s temperature has gone up $0.5^\circ$ in the last 15 minutes. She is receiving one unit of packed RBC, one unit of apheresis platelets and one unit of fresh frozen plasma. She is also complaining of cold and chills. What should you do?  
   a. Give her a warming blanket  
   b. Slow down the transfusion rate  
   c. Stop the transfusion immediately  
   d. Nothing—everything seems normal  

**Answer: C**

8. Which of the following should **NOT** be infused in the same line with any blood component.  
   a. 5% dextrose in water (D5W)  
   b. 0.2% saline  
   c. Normal saline  
   d. Ringer’s solution  

**Answer: B**
9. A first-time donor comes into the blood bank and has a few questions. She asks whether her blood will be tested for bacteria and viruses. Which of the following pathogens is not routinely tested for?
   a. Hepatitis
   b. Treponema
   c. Enterovirus B
   d. CMV
   
   **Answer: C**

10. An acute hemolytic reaction during a transfusion for acute blood loss is most likely due to:
   a. ABO incompatibility
   b. Too rapid infusion
   c. Rh0D incompatibility
   d. Massive sepsis

   **Answer: A**
REFERENCE SECTION

The reference section of in-text citations include published works intended as helpful material for further reading. Unpublished works and personal communications are not included in this section, although may appear within the study text.


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