NEW YORK STATE
COUNCIL ON HUMAN BLOOD AND TRANSFUSION SERVICES

AND

NEW YORK STATE
BOARD FOR NURSING

Appendix B

Transfusion Reaction Fact Sheets

Table of Contents

Acute Reactions

Delayed Reactions

Appendix B

Transfusion Reaction Fact Sheets

Acute Reactions

<table>
<tr><th colspan="3">Acute Hemolytic Reactions (< 24 Hours)</th></tr>
<tr><th>Clinical Presentation</th><th>Pathophysiology</th><th>Treatment</th></tr>
<tr><td rowspan="2">• Fever ≥ 1°C(2°F)
• Rigors, chills
• Nausea
• Lower back/flank pain
• Chest pain or tightness
• Hypotension
• Tachycardia
• Tachypnea
• Shock
• Pain at infusion site or along infusion vein
• Anxiety
• Unexplained bleeding from mucous membranes or infusion sites
• Hemoglobinuria
• Hemoglobinemia
• Oliguria/anuria
• Renal failure
• Disseminated intravascular coagulation (DIC)
• Laboratory evidence of acute hemolysis
• Direct antiglobulin test (DAT) may be positive or negative</td><td rowspan="2">Incompatible blood administration results in an antigen/antibody response with activation of complement and subsequent intravascular hemolysis. Acute hemolytic reactions usually involve the ABO blood system. Misadministration of blood often results from improper identification of transfusion recipients, either at the time of phlebotomy for the type and screen specimen or at the time of transfusion. Occasionally, acute hemolysis may occur from mixing of blood with a fluid other than normal saline or from improper warming or freezing of blood. Acute hemolytic reactions can also result from administration of incompatible plasma. Acute hemolysis has also been reported with use of IV RhIG for immune thrombocytopenic purpura (ITP).</td><td>• Stop transfusion
• Maintain airway; provide oxygen and ventilatory support if necessary
• Hydration to maintain renal function
• Cardiovascular support with pressor agents, as indicated (pressor agents that decrease renal blood flow are contraindicated)
• Diuretics to promote renal perfusion
• Treat DIC
• Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimens
• Do not initiate another transfusion without Blood Bank consultation
• Document reaction in patient’s chart as per institution policy</td></tr>
<tr><td>Prevention
• ABO mistransfusions may be avoided by proper patient identification
• Administer blood with only normal saline
• Using ABO compatible platelets or group O platelets with low anti-A/B titers to non-group O recipients</td></tr>
</table>

Sepsis/Bacterial Contamination

Clinical Presentation	Pathophysiology	Treatment
• Fever, often ≥ 2°C (4°F) • Chills • Rigors • Hypotension • Shock • Renal failure • Unexplained bleeding from mucous membranes or infusion sites • Disseminated intravascular coagulation (DIC)	Sepsis is the result of transfusion of bacterially contaminated blood components. The bacteria usually originate from the blood donor, either from venipuncture (*e.g., Staphylococcus, Streptococcus)* or from unsuspected bacteremia (*e.g., Yersinia),* but may also result from donor unit processing. Bacterial multiplication is more likely to occur in components stored at room temperature (*e.g.,* platelets) than in components stored at refrigerator temperatures (*e.g.,* red cells).	• Stop transfusion • Maintain airway; provide oxygen and ventilatory support if necessary • Hydration to maintain renal function • Cardiovascular support with pressor agents, as indicated • Treat DIC • Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimens • Do not initiate another transfusion without Blood Bank consultation • Send implicated blood component to the lab for Gram stain and culture • Draw blood culture from patient • Promptly initiate IV antibiotics if indicated by the Gram stain results • Document reaction in patient's chart as per institution policy
		Prevention
		• Platelet components should be tested for bacterial contamination • Visual inspection of units for color changes, hemolysis, clots • Units should be started promptly upon issuance • Blood and components should be transfused within 4 hours after the unit is entered • Tubing should be changed between blood units as per policy

Transfusion-Related Acute Lung Injury (TRALI)

Clinical Presentation

- Rapid onset of acute respiratory distress during or within 6 hours after transfusion (usually of plasma-containing components)
- Dyspnea
- Cyanosis
- Hypoxemia (O_2 sat ≤ 90% on room air or P_aO_2 ≤ 300 mm Hg)
- No evidence of circulatory overload (left atrial hypertension)
- Hypotension or, in some cases, hypertension
- Fever
- Tachycardia
- Transient leukopenia
- Bilateral pulmonary infiltrates on chest x-ray
- Most patients improve over 2-3 days
- Mortality rate about 10%
- Normal brain natriuretic peptide (BNP)

Pathophysiology

TRALI most commonly results from the infusion of donor antibodies directed against recipient human leukocyte antigen (HLA) or human neutrophil antigen (HNA) antigens. Neutrophil activation causes capillary leakage and pulmonary damage. Infrequently, recipient antibodies against cognate donor leukocyte antigens may be implicated.

In a number of TRALI cases, no antibody is found. Biological response modifiers may be implicated in these cases.

TRALI may occur with any blood component, but it occurs more commonly with components containing large volume of donor plasma. Donors of implicated units are usually multiparous females who have been immunized to HLA or HNA antigens via pregnancy.

Other risks for acute lung injury include: direct lung injury (aspiration, pneumonia, toxic inhalation, lung contusion, near drowning), indirect lung injury (severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, drug overdose).

Treatment

- Stop transfusion
- Maintain airway; provide oxygen and ventilatory support if necessary
- Treat hypotension; cardiovascular support; pressor agents if needed
- Diuretics and steroids are generally not helpful and may be contraindicated
- Do not initiate another transfusion without Blood Bank consultation
- Document reaction in patient's chart as per institution policy

Additional Testing

- Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimen
- Normal BNP can help distinguish from transfusion-associated circulatory overload (TACO), but elevated BNP can be seen in both TRALI and TACO
- The blood collection facility should be notified. The patient and donor(s) should be worked-up using an appropriate algorithm. The donor should be tested for the presence of HLA and/or HNA antibodies. If present, these should be compared to the patient's phenotype

Prevention

- Implicated donors are evaluated prior to future donations
- Other TRALI mitigation strategies include use of blood components, such as platelets, with a lower volume of plasma

Future Transfusion

- Patients are not generally at risk for recurrence
- Because HLA antibodies are more common in female donors, many centers are providing plasma from donors who are male, a nulliparous female, or who have been screened for antibodies

Moderate (Anaphylactoid) and Severe (Anaphylactic) Allergic Reactions

Clinical Presentation	Pathophysiology	Treatment
• Wheezing, stridor, dyspnea (respiratory distress) • Bronchospasm • Cyanosis • Hypotension • Tachycardia • Urticaria • Pruritis • Flushing • Gastrointestinal distress • Shock • Erythema and edema of the periorbital area • Angioedema • Rash • No fever	The transfusion recipient has an antibody that may be an IgE directed against an antigen in donor plasma, such as an IgA-deficient patient who possesses antibodies to IgA. The cause, however, is often not identified.	• Stop transfusion • Maintain airway; provide oxygen and ventilatory support if necessary; intubate if significant upper airway obstruction • Treat hypotension - Trendelenburg position and fluids; epinephrine if unresponsive • Treat with antihistamine • Moderate reactions may require steroids or other medications as necessary • Do not initiate another transfusion without Blood Bank consultation • Document reaction in patient's chart as per institution policy **Additional Testing** • Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimen(s) • Send a specimen for IgA level, if clinically indicated. If low, send patient sample for anti-IgA testing **Future Transfusion** • Patient may be given diphenhydramine or steroids prior to transfusion • IgA-deficient patients can be given washed cellular components or components from IgA-deficient donors, although such donors are rare and components may be difficult to obtain • Use washed or deglycerolized RBCs (or washed platelets) for patients experiencing severe reactions not caused by anti-IgA. Consider storing autogeneic units for future plasma transfusions

Transfusion-Associated Circulatory Overload (TACO)

Clinical Presentation	Pathophysiology	Treatment
• Dyspnea • Orthopnea • Cough • Cyanosis • Headache (severe) • Tachycardia • Hypertension • Congestive heart failure (left heart failure) • Rales on auscultation • S3 may be present • Bilateral pulmonary edema on chest x-ray • Increased central venous pressure • Temperature not elevated • Neck veins may be distended • White blood cell count unchanged	TACO is a life-threatening condition due to rapid increases in blood volume in patients with compromised cardiac or pulmonary function and/or in patients with chronic anemia and expanded plasma volume. Infants and adults > 60 years in association with rapid transfusion are most at risk. It may also be caused by infusion of 25% albumin (oncotic pressure causes shift of fluid from extravascular to intravascular space). Transfusion-associated dyspnea: Respiratory distress occurs within 24 hours of transfusion completion, but does not meet criteria for TRALI or TACO. Not otherwise explained by the patient's underlying or pre-existing medical condition.	• Stop transfusion • Upright posture • Maintain airway; provide oxygen and ventilatory support if necessary • Diuretics (*e.g.*, furosemide) • Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimen(s) • Do not initiate another transfusion without Blood Bank consultation. Circulatory overload must be addressed prior to initiation of additional blood components or volume expanders • Document reaction in patient's chart as per institution policy **Additional Testing** • Elevated brain natriuretic peptide (BNP) can also be seen in TRALI **Future Transfusion** • Except in conditions of ongoing rapid blood loss, blood components should be administered to at-risk patients slowly (1mL/kg/h) with attention to total fluid input and output; if extended periods of transfusion are required, request split units • Diuretics may be given prior to or during the transfusion

Hypotensive Transfusion Reactions

Clinical Presentation	Pathophysiology	Treatment
• Hypotension during or within one hour of transfusion (usually occurs <15 minutes after initiation) • Adults (≥18 years): Drop in systolic BP of ≥ 30 mmHg **and** systolic BP ≤80 mmHg • Children and adolescents (<18 years old): >25% drop in systolic BP (*e.g.,* drop in baseline systolic BP of ≥120 mmHg to <90 mmHg) • Neonates and small infants (<1 year old OR any age and <12 kg body weight): >25% drop in baseline value using whichever measurement is being recorded (*e.g.,* mean BP) • Other symptoms, such as facial flushing, dyspnea, or abdominal cramps may occur, but usually hypotension is the sole manifestation.	Hypotensive transfusion reactions are thought to be mediated by bradykinin (BK), a vasoactive kinin generated by activation of the contact system, which occurs when plasma comes in contact with a negatively charged surface, such as a bedside leukoreduction filter or apheresis device. Bradykinin has potent vasodilatory effects, causing a marked reduction in peripheral vascular resistance. Angiotensin converting enzyme (ACE) is part of the degradation pathway that transforms bradykinin into inactive metabolites, and patients on ACE inhibitors, which impair bradykinin inactivation, are particularly at risk.	• Stop transfusion; responds rapidly (within 10 minutes) to cessation of transfusion and supportive treatment • Treat hypotension – Trendelenburg position and fluids; pressor agents, if unresponsive • Maintain airway; provide oxygen and ventilatory support if necessary • Do not initiate another transfusion without Blood Bank consultation • Document reaction in patient's chart as per institution policy **Additional Testing** • Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimen(s) **Prevention** • Discontinue ACE inhibitors • Avoid bedside leukoreduction filters

Febrile Nonhemolytic Reactions

Clinical Presentation	Pathophysiology	Treatment
• Temperature rise of ≥ 1°C (2°F) during or within 4 hours after transfusion, without any other obvious cause • Chills/rigors with or without fever • Headache • Nausea/vomiting • Tachycardia, palpitations, and cough may also occur	Preformed anti-HLA antibodies in the recipient (from pregnancy or previous transfusion) react with corresponding antigens on transfused white blood cells, triggering cytokine release. Alternatively, preformed cytokines from white blood cells in the donor units may be directly infused. Most febrile nonhemolytic reactions are benign, although some may cause significant discomfort and hemodynamic or respiratory changes.	• Non-salicylate antipyretic (acetaminophen) • Meperidine (injection) may be useful in patients with rigors • Do not initiate another transfusion without Blood Bank consultation • Document reaction in patient's chart as per institution policy **Additional Testing** • Initiate transfusion reaction work-up; send unit and administration set with attached solutions to the laboratory, in addition to blood specimen(s) **Future Transfusion** • Leukocyte-reduced (pre-storage) blood components may be indicated in patients with a history of febrile non-hemolytic transfusion reaction or who are chronically transfused • Premedication with acetaminophen has not been shown to be of benefit when leukocyte-reduced components are given

Mild Allergic Reactions

Clinical Presentation	Pathophysiology	Treatment
Skin • Urticaria • Itching • Flushing • Erythema	The transfusion recipient usually has an IgE antibody on mast cells directed against an antigen in donor plasma, resulting in activation and release of histamine. The majority of allergic reactions are mild.	• Stop transfusion • Diphenhydramine • In the case of mild reactions, the transfusion may be restarted after treatment, provided unit can be completed within 4 hours after the unit is entered • If symptoms persist or worsen, consider methylprednisolone or prednisone • Do not restart unit if urticaria is severe or patient develops significant local swelling, respiratory or gastrointestinal symptoms, or hypotension • Monitor closely for any other signs or symptoms • Document reaction in patient's chart as per institution policy **Future Transfusion** • Patient may be given antihistamine (diphenhydramine) prior to transfusion • If antihistamine is insufficient, hydrocortisone one hour prior to transfusion may be helpful • In cases of recurrent or severe reactions, washed or deglycerolized frozen red cells may be useful

Delayed Reactions

Transfusion-Associated Graft-vs.-Host Disease (TA-GVHD)

Clinical Presentation

- Fever
- Diarrhea
- Vomiting
- Rash (maculopapular)
- Hepatitis (elevated liver function tests) with hepatomegaly
- Refractory pancytopenia with bleeding and infectious complications
- Symptoms typically appear 8-10 days following transfusion (range 3-30 days)
- Rapid progression with virtually 100% mortality
- The median time to onset of symptoms is longer in the neonate (28 days) than in adults and the time to death longer for neonates (51 days) than adults (21 days)

Pathophysiology

TA-GVHD can occur when donor T-lymphocytes mount an attack against the recipient's tissues, causing enterocolitis, rash, and pancytopenia. The donor lymphocytes see the recipient tissues as foreign, but the recipient lymphocytes are not able to attack the donor lymphocytes. Because of resultant marrow aplasia, patients succumb, primarily from sepsis.

TA-GVHD is rare and is observed almost exclusively in immuno-compromised patients who have received blood from a relative.

The diagnosis is proven by demonstration of donor-derived lymphocytes in recipient's peripheral blood or tissues (by HLA typing).

Treatment

- Immunosuppressive agents (corticosteroids, cytotoxic agents, intravenous immune globulin)
- Treatment is usually not successful
- Hematopoietic progenitor cell transplant is potentially curative

Additional Testing

- HLA typing will reveal circulating lymphocytes of a different type than patient's type

Prevention

- Irradiation prevents TA-GVHD by rendering donor lymphocytes unable to replicate
- Identify patients at increased risk. Such patients should receive irradiated cellular components (see *Guidelines for Irradiation of Blood and Blood Components*)
- Directed blood donations (cellular components) from blood relatives and cellular components from donors selected for HLA compatibility or crossmatched should be irradiated
- Granulocyte components should be irradiated

Delayed Hemolytic Reactions (> 24 Hours)

Clinical Presentation	Pathophysiology	Treatment
• Fever • Jaundice • Hemoglobinuria/oliguria/anuria • Back/flank pain • Reaction typically occurs 3-7 days after transfusion, but may occur up to 28 days after transfusion • Patient may be asymptomatic • Direct antiglobulin test (DAT) may be positive and an antibody, not detected prior to the transfusion, may be identified • Laboratory evidence of hemolysis	A patient has made an antibody against a red blood cell (RBC) antigen in the remote past. Over time, the titer of this antibody has decreased to below detectable levels, so the antibody screen performed prior to the current transfusion does not detect the antibody. Administration of antigen-positive blood presents a second challenge to the immune system and provokes an anamnestic response. Hemolysis is usually extravascular; however, it may be intravascular. Without evidence of hemolysis, delayed serologic transfusion reactions are evident only by identification of new, significant RBC alloantibodies 1-28 days post-transfusion. Consider other causes, such as hyperhemolysis syndrome and transfusion-associated babesiosis, if hemolytic anemia occurs more than one week posttransfusion.	• Monitor renal function • Document reaction in patient's chart as per institution policy **Additional Testing** • Send a new blood specimen for antibody screen, antibody identification and DAT **Future Transfusion** • Transfuse with antigen-negative blood, as indicated

Posttransfusion Purpura (PTP)

Clinical Presentation	Pathophysiology	Treatment
• Thrombocytopenia, decrease to <20% of pre-transfusion count, occurring with abrupt onset 1-2 weeks after a transfusion • Melena • Hematuria • Vaginal bleeding • Occurs most commonly in multiparous women • Usually self-limited (≤ 2 weeks), but bleeding may be severe and can be fatal (*e.g.,* intracranial bleeding)	Thrombocytopenia occurs in a patient who has made an antibody against a foreign platelet antigen as a result of pregnancy or a previous transfusion. After a transfusion of red cells or platelets, antibodies attach to surface antigen sites on platelets, resulting in their destruction by splenic and hepatic macrophages. Most commonly, the implicated antibody is against the HPA-1a (PL^{A1}) antigen (60% of cases). Through a mechanism not clearly elucidated, the patient's own antigen-negative platelets are also destroyed.	• Intravenous immune globulin (IVIG) • Plasma exchange with FFP replacement, if refractory to IVIG • Document reaction in patient's chart as per institution policy • Transfusion of antigen-negative platelets is generally ineffective **Testing** • Platelet antibody screen may reveal HPA-1a specific antibody in patient serum • Platelet antigen type (phenotype or genotype) may reveal that patient is HPA-1a negative **Future Transfusion** • Repeat reactions are rare • If platelet transfusion is needed, platelet typing of family members may help identify potential antigen-negative donors