Complications of Transfusion

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What is a transfusion reaction?

- Includes any adverse reaction to transfusion
- Can present with a broad range of symptoms
- The same symptoms may be seen with different types of reactions
- Some symptoms (i.e. fever) could be the first sign of a mild reaction or a life-threatening reaction
- Because it is impossible to determine at the time which type of reaction is occurring

**the transfusion MUST BE STOPPED for any reaction.**

*(Except isolated hives.)*
Is it really that bad? Yes.

Figure 1: Transfusion-Related Fatalities by Complication, FY2010 through FY2014

“Fatalities reported to the FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2014.”
Good News

• Transfusion reactions usually fit into a recognizable category that experts agree on
  – Examples: allergic, bacterial

• Recognizing patterns has allowed us to detect and even prevent reactions

• Timely and accurate recognition results in appropriate ancillary testing and clinical response
Bad News

• The US is slow to catch up to other nations regarding standardized definitions and required reporting of reactions
• Most transfusion services do not have explicit definitions for each reaction
• With multiple pathologists taking call at most sites, there is opportunity for inconsistency
Lab Work-Up

• Clerical check
• Direct Anti-globulin Test (DAT)
• Check for visible hemolysis
• +/- Check for urine hemoglobin
Lab Work-Up

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- Direct Anti-globulin Test (DAT)
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Interpretation?
Ancillary tests?
Transfusion recommendations?
National Healthcare Safety Network
Hemovigilance Module

• Introduced by the CDC in 2009
• Purpose = national surveillance of transfusion associated adverse events
• Goals =
  – Improve patient safety
  – Minimize morbidity and mortality
  – Identify emerging complications and pathogens
• Requires a common definition of each reaction type
Getting Involved

• Any facility where patients receive transfusions may participate
• Training is required (online or in-person)
• Reporting to CDC does **NOT** replace mandatory or regulatory reporting requirements of the FDA, your state, or other regulatory agencies.
• To get started, it is necessary to determine if your facility is enrolled in another NHSN program. Likely, the answer is yes, via infection prevention.
Benefits of Participation

- Uniform reporting and documentation of facility adverse events, which may lead to better monitoring and easier identification of areas needing intervention
- Access to CDC aggregate surveillance data for peer-to-peer comparisons
Hemovigilance Module Key Terms

- **Adverse event**: An unintended and undesirable occurrence before, during or after transfusion of blood or blood components. Includes incidents and adverse reactions.

- **Adverse reaction**: An undesirable response or effect in a patient temporally associated with the administration of blood or blood components. It may or may not be the result of an incident.

- **Incident**: Any error or accident that could affect the quality or efficacy of the blood, blood components, or patient transfusions. It may or may not result in an adverse reaction.

- **Near miss**: A subset of incidents that are discovered before the start of a transfusion that *could* have led to a wrongful transfusion or adverse reaction.
Figure 1. Venn diagram of NHSN Hemovigilance Module surveillance terms.

- **Transfusion-Related Activities**
  - Patient Sample Collection
  - Sample Handling and Testing
  - Inventory Management
  - Patient Monitoring

- **Transfusion**
  - Number of Components
  - Number of Patients

- **Adverse Events**
  - **Reactions**
  - **Incidents**
    - Near Miss Incidents
    - Incidents Related to Transfusion (No Adverse Reaction)
    - Incidents Related to Transfusion and Adverse Reaction
Data Reporting Requirements

• At least 12 months of continuous surveillance
• An annual facility demographic and practice survey for each calendar year
• ALL adverse reactions that follow transfusion at or by your facility
• ALL incidents (ie errors or accidents) associated with an adverse reaction
• The number of blood components transfused or discarded and patient samples collected for type and screen or crossmatch each month
Reporting Adverse Reactions

• All CDC defined adverse reactions that are possibly, probably or definitely related to a transfusion performed by the participating facility must be reported
• Reports should be made after investigation is complete
• Reports should be made within 30 days
• Adverse reactions must be classified according to CDC Hemovigilance Protocol
Using the HSHN Protocol

• Research by the AABB has shown this classification system is difficult for even trained participants to apply (AuBuchon, 2014)
  – 60 – 70% matched “expert” classification of fictional adverse events

• May be attributable to the fact that surveillance definitions do not always match clinical definitions.
CDC Defined Adverse Reactions

- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated dyspnea (TAD)
- Allergic reaction
- Hypotensive transfusion reaction
- Febrile non-hemolytic transfusion reaction (FNHTR)
- Acute hemolytic transfusion reaction (AHTR)
- Delayed hemolytic transfusion reaction (DHTR)
- Delayed serologic transfusion reaction (DSTR)
- Transfusion-associated graft vs. host disease (TAGVHD)
- Post-transfusion purpura (PTP)
- Transfusion-transmitted infection (TTI)
Reporting Criteria

• Case definition:
  – Definitive, probable, or possible

• Severity:
  – Non-severe, severe, life-threatening, death or not determined

• Imputability:
  – Definitive, Probable or Possible
  – Optional categories include doubtful, ruled-out and not determined.
Transfusion Associated Graft Versus Host Disease (TA-GVHD)

- Viable lymphocytes in transfused blood engraft in recipient and attack host tissues
- Usually immunocompromised recipient
- Can happen in immunocompetent recipients when donor HLA is not recognized as foreign
- ~100% fatal
- No treatment
- **Irradiation** is used to prevent this complication
Transfusion Associated Graft Versus Host Disease (TA-GVHD)

• Clinical syndrome that occurs 2 days to 6 weeks following cessation of transfusion including
  – Characteristic rash
  – Diarrhea
  – Fever
  – Hepatomegaly
  – Liver dysfunction
  – Marrow aplasia
  – Pancytopenia

• **And** characteristic histologic appearance of liver biopsy
Transfusion Related Acute Lung Injury

• Non-cardiogenic pulmonary edema
• Caused by a combination of
  • Donor antibodies against HLA or granulocyte specific antigens
  • “Priming” of neutrophils by a stress event (i.e. sepsis, surgery, etc.) which makes them stick to capillary walls in lungs
• Chest X-ray helpful in diagnosis
• Managed with supportive care
  • Oxygen by nasal cannula (100%), ventilation (75%)
  • Mortality est. 5 – 10%
• May be confused with anaphylaxis, TACO and transfusion-related sepsis.
Transfusion Related Acute Lung Injury

• No evidence of acute lung injury prior to transfusion **and**
• Onset within 6 hours of transfusion **and**
• Hypoxemia (<90% O₂ sat) **and**
• Radiographic evidence of bilateral infiltrates **and**
• No evidence of circulatory overload
Transfusion Related Acute Lung Injury

• Lab work up includes HLA (+/- Human Neutrophil Antigen) typing of recipient and testing of donor for anti-HLA (+/- anti-HNA) antibodies
  • Donors form antibodies in response to exposure to foreign HLA/HNA via pregnancy or transfusion

• Any splits of the unit must be withdrawn

• Implicated donor permanently deferred
Transfusion Related Acute Lung Injury

• Fatalities from TRALI should be reported to CBER in accordance with 21 CFR 606.170(b).
  • Must notify by phone, fax, mail or email “as soon as possible”
  • Written report due within 7 days of fatality

• The FDA encourages voluntary reporting of TRALI as a serious adverse reaction to transfusion.
Transfusion Associated Circulatory Overload

• Due to the administration of too much fluid or too rapid administration of fluid
• Patients with small blood volume (children) and compromised cardiovascular systems are at greatest risk
• Shortness of breath, edema, hypertension, and congestion on chest x-ray are symptoms
• Responds to diuretic treatment
• Supportive measures include oxygen
Transfusion Associated Circulatory Overload

• New onset or worsening of or more of the following:
  – Acute respiratory distress
  – Elevated BNP
  – Elevated central venous pressure
  – Evidence of left heart failure
  – Evidence of positive fluid balance
  – Radiographic evidence of pulmonary edema
AABB Standards on TACO

• Standard 5.19.7
  – “The BB/TS shall have a policy for responding to requests for product for patients identified by the ordering physician or other authorized health professional as being at increased risk for TACO.”

• Do you have a written policy that addresses TACO?
Transfusion Associated Dyspnea (TAD)

• Acute respiratory distress occurring within 24 hours of cessation of transfusion AND
• Allergic reaction, TACO, and TRALI are not applicable
• “Bucket” category to catch reactions that don’t quite meet threshold for above categories and emerging reactions.
Acute Hemolytic Transfusion Reaction

- Frequency estimated at 1/10,000 – 50,000 units
- Patient usually lives if prompt recognition occurs; reaction severity depends on strength of antibody and amount of blood transfused
- Most fatalities associated with > 200 mL transfusion
- Most common cause = failure to correctly identify recipient
- Commonest site of error = operating room
Acute Hemolytic Transfusion Reaction

- May be caused by ABO incompatibility or other blood group incompatibilities
  - Usually ABO antibodies in recipient, but rare cases of high titer O cells transfused to A, B or AB patients have been reported to cause hemolysis
- Recipient antibodies react against antigen on donor cells
- Complement is activated
- Intravascular hemolysis ensues
- Disseminated intravascular coagulation and renal failure occur
- Can present in a variety of ways:
  - “sense of impending doom” often reported, fever, flank pain, hematuria, severe hypotension
Acute Hemolytic Transfusion Reaction

• The more blood that is given, the worse the reaction is and the more likely the patient is to die.

• Patient Management
  – Fluids given to help maintain renal function
  – Drugs to maintain renal function
  – Medications given to support blood pressure if needed
  – Debatable: alkalinization of urine, transfusion of blood products, heparin
Acute Hemolytic Transfusion Reaction

• Occurs during or within 24 hours of cessation of transfusion with new onset of ANY of the following:
  • Back/flank pain
  • Chills/rigors
  • Disseminated intravascular coagulation
  • Nosebleed
  • Fever
  • Hematuria
  • Hypotension
  • Oliguria/anuria
  • Pain/oozing at IV site
  • Renal failure
  • AND
Acute Hemolytic Transfusion Reaction

• Two or more of the following:
  • Decreased fibrinogen
  • Decreased haptoglobin
  • Elevated bilirubin
  • Elevated LDH
  • Hemoglobinemia
  • Hemoglobinuria
  • Plasma discoloration consistent with hemolysis
  • Spherocytes on blood film
• **AND EITHER**
Acute Hemolytic Transfusion Reaction

**Immune mediated:**
- Positive DAT for anti-IgG or anti-C3
- **AND** positive elution test with antibody present on transfused cells

**Non-Immune mediated:**
- Serologic testing is negative
- Physical cause is confirmed
  - Thermal
  - Osmotic
  - Mechanical
  - Chemical
Drug Mediated AHTRs

• 1/ 1 million transfusions
• Many drugs have been implicated
• Drugs may induce formation of antibody
  – Against drug itself
  – Against red cell membrane components
  – Or against a combo antigen
• DAT may be + or –
• +/- Immune mediated destruction
Drug Mediated AHTRs

• Treatment
  – Supportive
  – Discontinue suspected drug

• Testing
  – May need to send out for special testing
  – DAT in presence of drug
  – If drug association has already been reported, testing may be available through your reference lab
Non-Immune Causes of AHTRs

• Thermal
  – Red cells destroyed if exposed to > 50\(^\circ\) C.
  – Reports of warming units in a water bath or microwave (!)
  – Blood may be accidentally frozen, causing hemolysis. Can cause cardiac arrhythmia if blood is too cold when infused.

• Osmotic
  – IV or surgical introduction of distilled water
  – Insufficiently deglycerolized red cells
Non-Immune Causes of AHTRs

• Mechanical
  – Transfusion of cells with intrinsic membrane defects
  – Transfusion through a narrow gauge needle

• Chemical
  – Transfusion concurrent with fluids other than normal saline
Delayed Hemolytic Transfusion Reaction

- Estimated at 1/1,500 – 12,000 transfusions
- May be fatal, especially with large volume transfusion
- Very similar to acute hemolytic transfusion reaction, except complement is not activated.
- RBC destruction is extravascular (in the spleen)
- Clinical symptoms are much milder and may not be present at all
- Lab confirmation: +DAT, ↓hemoglobin, ↑LDH, ↓haptoglobin, ↑visible hemolysis in serum and urine, + eluate
Delayed Hemolytic Transfusion Reaction

- Positive DAT for antibodies developed between 24 hours and 28 days after cessation of transfusion
- **And either** positive elution test with antibody on transfused RBCs
- **Or** newly identified red blood cell antibody
- **And either** inadequate post transfusion rise in hemoglobin levels or rapid fall back to pre-transfusion levels
- **Or** otherwise unexplained appearance of spherocytes
Delayed Hemolytic Transfusion Reaction

- Paradoxically, no free antibody may be detected for several days post transfusion
- Autoantibodies have been reported to arise in the situation of DHTR, complicating the workup
Delayed Serologic Transfusion Reaction

- Estimated at 1/3,000 transfusions
- Absence of clinical signs and symptoms of hemolysis and
- Demonstration of new antibodies against RBCs by either
  - Positive DAT
  - Positive antibody screen
- Definition is highly dependent upon what is clinically sought (daily bilirubin, icterus?)
Transfusion Transmitted Infection

- Bacterial infection
  - Thought to be caused by
    - Asymptomatic bacteremia in donor
    - Introduction of skin flora from skin plug during phlebotomy of donor
    - Contamination during processing
  - Platelets are by far the most commonly implicated product for bacterial contamination
  - Bacterial sepsis will usually present with acute shock during transfusion
- Other infections are carried in the plasma or the white cells and usually present later
Transfusion Transmitted Infection

- Laboratory evidence of a pathogen in a transfusion recipient

Pathogens of well-documented importance in blood safety.

These pathogens have public health significance for hemovigilance, are well-documented blood stream pathogens, and/or are routinely screened for in blood donors. A full list of potentially infectious organisms is available in the drop-down pathogen list in NHSN.

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Viral</th>
<th>Parasitic</th>
<th>Other</th>
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<tbody>
<tr>
<td>Enterobacter cloacae</td>
<td>Cytomegalovirus (CMV)</td>
<td>Babesiosis (Babesia spp.)</td>
<td>Creutzfeldt-Jakob Disease, Variant (vCJD)</td>
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<tr>
<td>Escherichia coli</td>
<td>Enterovirus spp.</td>
<td>Chagas disease&lt;br&gt;(Trypanosoma cruzi)</td>
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<tr>
<td>Klebsiella oxytoca</td>
<td>Epstein Barr (EBV)</td>
<td>Malaria (Plasmodium spp.)</td>
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<tr>
<td>Klebsiella pneumoniae</td>
<td>Hepatitis A</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
<td>Hepatitis B</td>
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<td>Serratia marcescens</td>
<td>Hepatitis C</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>Human Immunodeficiency Virus 1 (HIV-1)</td>
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<tr>
<td>Staphylococcus epidermidis</td>
<td>Human Immunodeficiency Virus 2 (HIV-2)</td>
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<td>Staphylococcus lugdunensis</td>
<td>Human Parvovirus B-19</td>
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<tr>
<td>Syphilis (Treponema pallidum)</td>
<td>Human T-Cell Lymphotropic Virus-1 (HTLV-1)</td>
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<td>Yersinia enterocolitica</td>
<td>Human T-Cell Lymphotropic Virus-2 (HTLV-2)</td>
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<td></td>
<td>West Nile Virus (WNV)</td>
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<td><strong>Zika!</strong></td>
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</table>
Risk of Acquiring a Transfusion Transmitted Infection

- Hepatitis A = 1/ 10 million units
- Hepatitis B = 1/ 30,000 to 1/250,000 units
- Hepatitis C = 1/ 2 million units
- HIV = 1/ 2 million units
- HTLV = 1/ 2 million units
- Malaria = 1/ 4 million units
Spectrum of Allergic Reactions

- **Mild**
  - Rash or hives (1% of transfusions)
- **Severe (1/20,000 transfusions)**
  - Angioedema
  - Drop in blood pressure
  - Difficulty breathing
    - Includes cough
- Most commonly caused by allergy to protein in transfused plasma
Allergic Reaction

• 2 or more of the following:
  – Conjunctival edema
  – Edema of lips/tongue/uvula
  – Erythema & edema around eyes
  – Generalized flushing
  – Drop in blood pressure
  – Localized edema
  – Rash
  – Itching
  – Respiratory distress
  – Urticaria (hives)
Treatments for Allergic Reaction

• Little data to guide treatment of allergic transfusion reaction
• Benadryl (PO or IV Push)
  – Can give at time of reaction or as a preventative in person with history of allergic reactions
• Corticosteroids
• Epinephrine
• Oxygen, intubation
• Washed products
IgA Deficiency and Transfusion

• Selective IgA deficiency is the most common primary immunodeficiency in the US
• Not all individuals who have clinical IgA deficiency have blood-bank concern-worthy IgA deficiency
• Class specific anti-IgA antibodies only develop in people with extremely low IgA (usually < 0.05 mg/dL)
• Routine IgA assays only go down to <7 mg/dL.
  – This is NOT sufficient testing to determine the patient’s risk of developing an anaphylactic reaction to blood products!
• Anti-IgA antibodies can occur naturally, so bad reactions can happen with the first transfusion.
Lab Workup of IgA Deficiency

• Ask, is this the patient’s first or second transfusion?
  – If the patient has been multiply transfused, this reaction is unlikely to be caused by IgA deficiency.

• Obtain in house IgA level, if available.

• If below detectable limit of in house assay, send out for highly-sensitive IgA level and anti-IgA antibodies.

• Very few labs do these tests and reagents sometimes go out of supply.
Prevention of Anaphylaxis in IgA Deficient Patients

• Frozen, deglycerolyzed RBCs
• Rare donor registry to obtain frozen plasma containing products
• Once identified, patients should wear medic alert band
• If plasma containing products are needed in an emergency, difficult decisions will need to be made
Other Proteins and Substances Implicated in Allergic Reaction

• Haptoglobin (seen in Asians)
• Environmental allergens such as dust, pollen, milk and egg
• Hypersensitivity reaction due to passively acquired (transfused) IgE antibodies from donor seen for environmental (horses, peanuts) and drug (penicillin) allergens
Hypotensive Transfusion Reaction

• All other adverse reactions presenting with hypotension are excluded AND hypotension occurs within 1 hour after cessation of transfusion

• Adults: drop in systolic BP $> 30$ mmHg and systolic BP $< 80$ mmHg

• Children 1 yr – 18 yr: Greater than 25% drop in systolic BP from baseline

• Neonates and small infants (less than 1 yr OR any age and $< 12$ kg): Greater than 25% drop in baseline value using whichever measurement is being recorded (eg mean BP)
Hypotensive Transfusion Reaction

- Exact etiology unknown
- May represent common feature of several reaction pathways
- One hypothesis:
  - Bradykinin is a peptide which causes vasodilation
  - Many patients are on ACE inhibitors
  - ACE normally regulates the amount of bradykinin through hydrolysis
  - Transfused plasma undergoes contact activation, generating even more bradykinin
  - With ACE function inhibited, vasodilation is promoted by increased bradykinin
Hypotensive Transfusion Reaction

- Bedside leukoreduction filters have been implicated, particularly in patients on ACE inhibitors
- However, many hypotensive reactions are observed in patients not on ACE inhibitors, not receiving blood through a leukocyte filter
Febrile Non-hemolytic Transfusion Reaction (FNHTR)

- Occurs within 4 hours of cessation of transfusion
- Fever ( > 38°C) **AND** a change of at least 1°C
- **OR** chills/rigors
- Most are benign, however fever can be the first sign of a severe reaction
- FNHTR is a diagnosis of exclusion
- Treated with antipyretics (Tylenol) and drugs to raise shivering threshold (Meperidine).
  - Such treatment not shown to mask serious reactions
Febrile Non-hemolytic Transfusion Reaction (FNHTR)

• Caused by anti-leukocyte antibodies in the recipient and/or accumulated cytokines in the blood product
• Cytokine release is the common event leading to fever
• Prestorage leukocyte reduction is an effective preventative tool
Post Transfusion Purpura

- Severe thrombocytopenia occurring in the first 3 weeks after transfusion in patient with history of exposure through pregnancy or transfusion
- Patient attacks foreign platelet antigen (usually HPA-1a)
- Patient’s own platelets are also destroyed
- Platelet count usually below 10,000
- Treatment is immunosuppression
Post Transfusion Purpura

• Alloantibodies in patient directed against specific antigens on platelets detected at or after development of thrombocytopenia

• **AND** thrombocytopenia
Post Transfusion Purpura

- Anti HPA-1a is the most commonly implicated antibody
- Uniquely, in addition to destroying foreign antigen bearing platelets, the recipient’s own antigen negative platelets are destroyed as well
- IVIG is first line treatment
- If transfusion is necessary, antigen negative platelets should be used, with recognition that decreased survival is expected
- Future transfusions should be with antigen negative units.
Post Transfusion Purpura

- Diagnostic testing
  - Many different methods for testing exist (flow cytometry, solid phase assay)
  - Key is to test for anti-platelet antibodies and to determine recipient genotype
  - Performed by a reference lab, with turn around time of ~ 1 week
Air Embolus

• Rare but life-threatening
• Not covered in NHSN guidelines
• Caused by air infusion in line
• Sudden shortness of breath, acute cyanosis, pain, cough, hypotension, abnormal heart rhythm
• Place patient on left side with legs above chest and head
Hypocalcemia

• Caused by rapid citrate infusion (massive transfusion, decreased citrate metabolism, apheresis)
• Perioral tingling, paresthesias, tetany, arrhythmia, seizure
• Diagnostic testing: ionized calcium, prolonged QT on electrocardiogram
• Oral calcium for mild symptoms, slow calcium infusion for more severe cases
Iron Overload

- Typically seen after > 100 units transfused
- Presents with diabetes, cirrhosis, cardiomyopathy
- Diagnostic tests: serum ferritin, liver enzymes, endocrine function tests
- Treatment: Iron chelation
References


Technical Manual, 18th edition. AABB.