Transfusion Reactions: Case Studies

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Objectives

1. Discuss the risks and adverse events associated with the transfusion of various blood products.

2. Compare and contrast the signs and symptoms associated with acute and delayed hemolytic and nonhemolytic transfusion reactions.

3. Given several patient case histories, correctly identify the most likely transfusion reaction and discuss the further testing and treatment indicated for each patient.
Case Study 1

- A 58-year-old, female patient receives 4 units of pRBCs and 4 units of FFP during surgery. Approximately 6 hours after the patient is returned to the SICU, her temperature is 38.6°C, her oxygen saturation is 85% (normal 95-100%), and she is having difficulty breathing.

- Within an hour, she is intubated and placed on supportive care.
Any adverse event related to the transfusion of a blood component.

- Acute (< 24 hours) vs. Delayed (> 24 hours)
- Febrile vs. Afebrile
- Hemolytic vs. Nonhemolytic
- Immune-mediated vs. Nonimmune-mediated
Concerns about Transfusion Safety

• Today, the blood supply is thought to be safer than it ever has been.

• Statistically, the greatest risk of mortality is not in the transmission of diseases.
  – Transfusion-related acute lung injury (TRALI)
  – Bacterial contamination
  – Hemolytic Transfusion Reaction (HTR)
- Clinical staff: nurses, physicians, transfusionists, etc.
  - Should be aware of signs and symptoms of a possible reaction.
  - Be prepared to take appropriate steps to mitigate the current episode AND prevent future similar reactions when possible.
    - Many common clinical signs and symptoms are associated with more than one type of adverse reaction
Transfusion Reactions

**Acute Febrile**
- Acute Hemolytic (AHTR)
- Acute Nonhemolytic (Febrile)
- Septic
- TRALI

**Acute Afebrile**
- Urticarial
- Anaphylactic
- Transfusion-associated Circulatory Overload (TACO)
- Premedicated

**Delayed Febrile**
- Delayed Hemolytic (DHTR)
- Transfusion-associated Graft vs. Host Disease (TA-GvHD)

**Delayed Afebrile**
- Post-transfusion Purpura (PTP)
- Iron Overload
• Presence of a fever.
• Acute febrile reactions occur *during or less than 24 hours* after transfusion and include the following:
  – Acute hemolytic reaction
  – Febrile nonhemolytic reaction
  – Bacterial contamination
  – Transfusion-related acute lung injury (TRALI)
Acute Hemolytic

- *Clerical error is #1 cause*
- Most common cause is ABO incompatibility of Donor RBCs with recipient. Rarely caused by incompatible Donor Plasma.
- Other causes include misidentification of anti-A1, anti-K, anti-Jk^a^, anti-Fy^a^.
- **Mechanical Hemolysis:**
  - IV gauge too small (must be 18-20 gauge or larger)
  - Malfunctioning blood warmer
  - Improper storage or processing
  - External pressure device
  - BP cuffs should never be used because they do not exert uniform pressure
  - Blood should only be transfused with saline—no medications or Lactated Ringer’s solution
Acute Hemolytic

• Presentation: fever/chills, back/flank pain, hemoglobinemia/uria, DIC

• Laboratory Workup
  – Check for clerical error
  – Visually inspect post-TXRN tube for hemolysis
  – Verify pre- and post-transfusion ABORh
  – DAT (a negative result does not always exclude hemolysis)

  – Additional tests:
    • Hgb/HCT
    • LDH
    • Bilirubin
    • Hemoglobinuria
    • Serum haptoglobin
• 1-2% of all transfusions
• Caused by accumulated cytokines (IL-6, TNF, etc.)
• Can be prevented by using pre-storage leukoreduced products.
• Clinical presentation: fever/chills, increase in temp >1°C
• Diagnosis: post transfusion reaction workup is normal
• Bacterial contamination of RBC: psychrophilic bacteria *Y. enterocolitica*, *Pseudomonas* spp., *E. coli* bacteria in donor’s blood or through collection site.

• Bacterial contamination of PLT occurs 1:3,000

• Can be prevented by Donor Center precautions, proper use of betadine or chlorhexidine and sterile technique.

• Pathogen Reduction
• Clinical presentation: Rapid high fever, rigors, shock
• Diagnosis: Gram stain, culture
# Bacterial contamination of blood products

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<tr>
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<th>pRBCs (1-6 degrees C)</th>
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<tr>
<td><strong>Yersinia enterocolitica</strong></td>
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<td><strong>Pseudomonas fluorescens</strong></td>
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<td><strong>Pseudomonas putida</strong></td>
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<td>Other bacteria</td>
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<tr>
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<th>Platelets (20-24 degrees C)</th>
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<td><strong>Staphylococcus epidermidis</strong></td>
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<td><strong>Salmonella choleraesuis</strong></td>
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<td><strong>Serratia marcescens</strong></td>
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<tr>
<td><strong>Staphylococcus aureus</strong></td>
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<td><strong>Bacillus cereus</strong></td>
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<td><strong>Streptococcus viridans</strong></td>
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<td>Other bacteria</td>
<td>36%</td>
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http://cdn.intechopen.com/pdfs-wm/27955.pdf
Pathogen Reduction

- The INTERCEPT™ blood system:
  - Inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites, and donor T cells (TA-GvHD prevention).
  - Amotosalen intercalates into DNA and RNA of pathogens and donor T cells.
  - Upon exposure to UVA light, amotosalen binds to and irreversibly blocks the replication of DNA and RNA.
  - Works for platelets and plasma.
  - Pathogen inactivation of RBCs requires a different mechanism because UVA light cannot penetrate to activate the amotosalen.
Pathogen Reduction (Plasma and Platelets)

Amotosalen

Nucleic Acid

UV light
• Transfusion-related Acute Lung Injury (TRALI) 1:1300-1:5000.
• Patients are often intubated; 20% fatal
• Thought to be caused by:
  – 1) Transfused anti-HLA and/or anti-HNA antibodies that activate PMNs
  – 2) Endothelial activation and PMN lung sequestration, then activation by blood substances
• Use only plasma from male donors to decrease HLA/HNA antibodies
• HLA screening of female PLT donors; deferred if positive
• Clinical presentation: Acute lung injury less than 6 hours after transfusion, bilateral CXR infiltrates, hypoxemia. No cardiac dysfunction.
• Post transfusion reaction workup is negative; positive diagnosis is difficult: donor HLA/HNA antibodies.
Immune-mediated TRALI

Caused by antibodies in the donor unit that react with the recipient’s white cells

- HLA-I: 4-23%
- HLA-II: 34-47%
- HNA: 8-28%

Lung illustration credit: Patrick J. Lynch, medical illustrator. Creative Commons Attribute 2.5
First hit: damage to the lung endothelium: infection, trauma, inflammation, etc., primes the endothelium and PMNs

Second hit: transfusion of blood component containing biologically active substances (cytokines, lipids, etc., and/or HLA/HNA antibodies activates the patient’s PMNs
Chest X-Ray

TRALI

Normal

Photo Credit: https://commons.wikimedia.org/wiki/File:Transfusion-related_acute_lung_injury_chest_X-ray.gif
Occur < 24 hours of transfusion that present without fever:

• Urticarial (mild allergic)
• Anaphylactic (severe allergic)
• Transfusion-associated circulatory overload (TACO)
• Premedicated febrile
Urticarial

- Urticarial (mild allergic reactions) occur in 1-3% of all units transfused
- IgE
  - Premedication with antihistamines
  - Washed blood
- Patient experiences localized or diffuse hives/redness
- Post transfusion reaction workup will be negative
Urticarial
Anaphylactic

- Most severe form of Type-I hypersensitivity reaction
- Generally appear shortly after the transfusion has been started and minimal volume has been transfused.
- Triggering factor is rarely identified
- Associated with **IgA or haptoglobin deficiency**
- Patient shows signs of severe hypotension, GI symptoms, swelling of throat (fevers are rare).
- Treatment may require epinephrine and intubation.
- Post transfusion reaction workup will be **negative**
• Post transfusion reaction workup is negative.
• Patients diagnosed by testing for presence of anti-IgA or anti-haptoglobin; checking IgA levels
• Requires 2 Liter wash of cellular products or IgA/haptoglobin deficient donors.
Transfusion-associated circulatory Overload (TACO)

- Transfusion associated circulatory overload (TACO) occurs 1:350-5,000 transfusions
  - Very old and very young patients are the most at risk
- **Cardiopulmonary disease** with too rapid blood infusion.
- Prevented by dividing blood into *aliquots, slow infusion*.
  - Dyspnea, hypoxia, pulmonary edema
- Post transfusion reaction workup is normal.

Aliquot photo courtesy of ARUP
## Compare and Contrast TACO and TRALI

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<th>Pulmonary</th>
<th>Cardio</th>
<th>Cause</th>
<th>Treatment</th>
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<tr>
<td><strong>TRALI</strong></td>
<td>Dyspnea</td>
<td>PMNs visible in lungs CXR</td>
<td>No cardiac involvement</td>
<td>Donor anti-HLA/-HNA attacks recipient WBCs</td>
<td>Intubation Supportive therapy</td>
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<td></td>
<td>Cough</td>
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<tr>
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<td>Cyanosis</td>
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<tr>
<td></td>
<td>Hypoxemia</td>
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<tr>
<td><strong>TACO</strong></td>
<td>Dyspnea</td>
<td>Pulmonary edema CXR</td>
<td>Tachycarida Hypertension</td>
<td>Volume overload</td>
<td>Diuretics, slow infusion, smaller volumes</td>
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<tr>
<td></td>
<td>Cough</td>
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<td>Cyanosis</td>
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<tr>
<td></td>
<td>Hypoxemia</td>
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</table>
Premedicated febrile

• Same as febrile nonhemolytic, but patient has been premedicated, fever is blocked by antipyretic.

• Chills; patient treated with meperidine if chills are violent.

• Post transfusion reaction workup is normal.
Transfusion Reactions

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Delayed Afebrile
- Post-transfusion Purpura (PTP)
- Iron Overload
Delayed Hemolytic Reactions occur 1:2500-11,000 transfusions.

- anti-K, anti-Jk\(^a\), anti-Fy\(^a\)
- Caused by an **anamnestic** response (rapid IgG production) to re-exposure to RBC antigen.
Delayed Hemolytic (DHTR)

- Prevented by *checking patient histories*. Patients should be informed whenever they have an unexpected antibody—encouraged to carry a card and inform physician.

- Patients are mobile and can be treated at many different facilities.

- Positive DAT, hyperbilirubinemia, IAT positive >2 days rapid increase in IgG.
TA-GvHD

• Rare complication of transfusion

• *Mortality is significant*; supportive therapy usually in vain. Fatality rate has been documented at 84% with a median survival period of 21 days post transfusion. Death usually caused by infection or hemorrhage secondary to bone marrow aplasia.

• Caused by cellular immune response by transfused T-lymphocytes vs. host.

• Symptoms 2-30 days after transfusion
  – Fever, diarrhea, skin rash
• Prevention: Irradiation of cellular products transfused to *at-risk recipients*:
  – lymphopenia, bone marrow suppression, intrauterine-transfused fetuses, newborns, congenital immunodeficiency syndrome, hematologic/oncologic disorders, patients receiving “directed donations” of RBCs from blood relatives.
Delayed afebrile

– Post-transfusion Purpura (PTP)
– Iron Overload
- Post-transfusion Purpura (PTP) occurs 1:24,000 transfusions, usually in *multiparous females*, 7-14 days after transfusion, PLT counts drop below 10,000/mm³.

- Rapid onset of thrombocytopenia as a result of anamnestic production of platelet alloantibody (usually HPA-1a) (anti-PLA¹) patient’s own platelets are also destroyed.
  - Patient sera should be tested for platelet-specific antibodies, HLA antibodies, and lymphocytotoxict antibodies.
Iron Overload

- **Transfusion hemosiderosis**
- Excessive iron deposition in recipient.
  - Each unit of RBCs has about 225 mg of iron.
- Patients with certain diseases are chronically dependent on RBC transfusion support:
  - congenital hemolytic anemias
  - aplastic anemia
  - chronic renal failure
### Transfusion Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Temporal Relationship</th>
<th>Severity</th>
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<tbody>
<tr>
<td>Anaphylactic</td>
<td>0-1 hour</td>
<td>Severe</td>
</tr>
<tr>
<td>Acute hemolytic</td>
<td>0-1 hour</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>TRALI</td>
<td>0-6 hours</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>Septic</td>
<td>0-6 hours</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>TACO</td>
<td>1-4 hours</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>Urticarial/Allergic</td>
<td>0-6 hours</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td>Febrile</td>
<td>1-6 hours</td>
<td>Mild</td>
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Time of Onset and Severity

<table>
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<tr>
<th>Type</th>
<th>Temporal Relationship</th>
<th>Severity</th>
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<td>TA-GVHD</td>
<td>Weeks</td>
<td>Severe</td>
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<tr>
<td>Alloimmunization</td>
<td>Days-months</td>
<td>None to Severe</td>
</tr>
<tr>
<td>Delayed Hemolytic</td>
<td>Days</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>Iron Overload</td>
<td>Years</td>
<td>Mild to Severe</td>
</tr>
<tr>
<td>PTP</td>
<td>Weeks</td>
<td>Moderate to Severe</td>
</tr>
</tbody>
</table>
• Citrate Toxicity
  – Plasma citrate levels may arise as blood products contain citrate as an anticoagulant. When large volumes are transfused rapidly, citrate can bind calcium and ionized calcium and result in hypocalcemia (manifesting particularly in liver dysfunction, hypothermic, or shock patients).
Metabolic Complications

• During storage, the intracellular potassium gradually leaks into the supernatant plasma or additive solution.

• Extracellular potassium load is:
  – 0.5 mEq for fresh RBC unit
  – 5-7 mEq for expired units
  – significantly elevated in **IRRADIATED** blood products

• Hyperkalemia can be a problem in patients with:
  – pre-existing hyperkalemia
  – renal failure
  – premature infants
  – newborns receiving large transfusions
  – cardiac surgery or exchange transfusion.
• Hypokalemia is observed more frequently than hyperkalemia after transfusion because potassium-depleted donor RBCs reaccumulate K+ ion intracellularly, and citrate metabolism causes further movement of potassium into the cells in response to the consumption of protons.
If a transfusion reaction is suspected

- Immediately stop the transfusion!
- Keep intravenous line open with normal saline.
- Blood component, attached tubing, solutions, and paperwork are to be returned to the blood bank for laboratory work up.
The workup

- Clerical checks
- Visual inspection of pre- and post-transfusion serum for evidence of hemolysis.
- Direct Coomb’s test (DAT)
- ABORh confirmation on Pre- and Post-TXRN samples
- If applicable:
  - Repeat Crossmatch
  - Repeat Ab screen on Pre- and Post-sample
  - Urine Test of first-voided post-transfusion specimen for presence of free hemoglobin (not for free RBCs.)
  - Hgb/HCT
  - LDH (increases as RBCs break down)
  - Haptoglobin (decreased if acute intravascular, normal if extravascular/delayed)
  - Bilirubin (*peaks in 3-6 hours as free hemoglobin is metabolized*)
Intravascular Hemolysis

Serum haptoglobin

Hemoglobininurea

Level

Time (days)

1 2 3 4 5 6 7
A 58-year-old, female patient receives 4 units of pRBCs and 4 units of FFP during surgery. Approximately 6 hours after the patient is returned to the SICU, her temperature is 38.6°C, her oxygen saturation is 85% (normal 95-100%), and she is having difficulty breathing.

Within an hour, she is intubated and placed on supportive care.
Case study 1
TXRN Workup

• Laboratory Results
  – Clerical Check: Correct
  – Pre-transfusion ABORh: A pos
  – Post-transfusion ABORh: A pos
  – Visual hemolysis: negative
  – DAT: negative

• Most consistent with ________________.

• What additional tests could be useful?
Case study 2

• A 35-year-old male patient is receiving a unit of ABO type-specific (noncrossmatched) pRBCs in the emergency room. Within 8 minutes of transfusion the patient exhibits the following vital signs:
  – Temp 38.2°C
  – Pulse 115
  – BP: 80/50

• A nurse practitioner calls the blood bank asking for help, and you answer. What do you tell the NP?
1. Stop the transfusion immediately
2. Keep the I.V. line open with Normal Saline (0.9)
3. Treat the patient
4. Send the unit of blood to the blood bank with all attached tubing and paperwork (crossmatch tag)
5. Draw samples for TXRN workup
6. In this case, would it be appropriate to perform urinalysis?
7. Notify Transfusion Services physician or designee with results.
Case study 2

• Lab results:
  – Clerical check: Correct
  – Pre-TXRN ABORh: B pos
  – Post-TXRN ABORh: B pos
  – Visual hemolysis: Positive
  – DAT: Positive

• What test(s) still need to be performed?
### Case study 2

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<tr>
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<th>37°C</th>
<th>AHG</th>
<th>CC</th>
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<tr>
<td>AC</td>
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SC= screening cell, AHG= antihuman globulin, CC=check cells, AC= autocontrol
# Case Study 2 Panel

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<tr>
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<th>Rh-Hr</th>
<th>Kell</th>
<th>Duffy</th>
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**AC**
Checkpoint

• Fever is present in which of the following transfusion reactions?
  A. TACO
  B. HTR
  C. TRALI
  D. Urticarial
Which of the following transfusion reaction diagnoses has the poorest outcome?

A. TACO
B. TA-GvHD
C. TRALI
D. Bacterial Contamination
Case study 3

• Packed red blood cells are ordered for two patients to be transfused on a medical-surgical unit of a 100-bed hospital in Utah.
  – Patient A: Jones, Charles
  – Patient B: Johnston, Wayne
• A nurse calls the blood bank to ask if crossmatched blood is available for patient Jones. The MLS replies that the blood is available for dispense.
• Shortly after, the nurse taking care of Johnston, Wayne asks the Health Unit Coordinator (HUC) to go pick up the blood for her patient.
Case study 3

• The HUC arrives in the blood bank and states, “I’m here to pick up blood.”

• After verifying the HUC is from med-surg, the MLS retrieves the blood from the crossmatch fridge for whom they recently received call from that floor.

• Verification of crossmatch tag and donor unit information are performed and the unit is dispensed.
Case study 3

- The HUC delivers the blood to the requesting nurse and the blood is transfused.
- Within a few minutes, the patient exhibits the following:
  - Chills with rigors
  - Fever
  - Back pain
  - Hypotension
Case study 3

• The transfusion is stopped.
  – What immediate steps should be taken?
    • Keep IV line open with normal saline, treat patient
    • Clerical check of the crossmatch tag/ re-identify patient
    • Notify the physician
Case study 3

- It is discovered that the blood intended for Jones was transfused to Johnston in error.
- The patient is immediately treated for an acute hemolytic transfusion reaction:
  - Urine output >1 mL/kg/hour with fluids and IV diuretic (furosemide)
  - Analgesics
  - Pressors to manage hypotension (low dose dopamine)
  - Management of bleeding due to DIC:
    - Platelets
    - CRYO
    - FFP
Take a few moments and identify problems in this scenario.

- *What steps could have been taken to prevent this?*
A 58-year-old male patient was admitted to the hospital to undergo cardiac bypass surgery. The pre-surgery type and screen were A, Rh-positive with a negative antibody screen. The patient’s transfusion history showed no previous transfusions although an antibody screen was performed over two years ago and was resulted as negative. The patient received three units of leukocyte-reduced packed red blood cells (pRBCs) during the day of surgery, and one additional unit the following day. All four units were crossmatched electronically.
My parrot—Icarus

Questions?