Common Reactions to Blood Transfusion

Grand Rounds
October 22, 2018
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PGY3
The history of the blood transfusion
Richard Lower
1631-1691

- First reliably documented successful transfusion
- Animal-to-animal
- February 1665
Dr. Jean-Baptiste Denys
1643-1704

- First animal to human transfusion
- Using blood of sheep, he transfused 4 patients in 1667
  - 2 survived (transfused small amount of blood)
  - 2 died (transfused multiple times)
Dr. Jean-Baptiste Denys
1643-1704

- Additionally in 1667, transfused the blood from a lamb into a “subject of a harmless form of insanity”
- Had been suggested that the “blood from a gentle lamb may quiet the tempestuous spirit of an agitated person”
- Heated controversy in 1668
- Banned by the royal society and French government
- Condemned by the Vatican in 1670
- Transfusion experimentation fell into obscurity for the next 150 years
James Blundell
Ob/Gyn FTW

- First successful transfusion of human blood following postpartum hemorrhage
- Used blood from patient’s husband
  - 4oz total
- Experiments continued through mid 1800’s, culminating with whole blood transfusion for hemophilia
The discovery of blood types

- Discovered by Dr. Karl Landsteiner in 1901
  - A, B, O
  - First to discover immune response and hemolysis when incompatible blood types are mixed
  - Allowed for identification of blood type and safer transfusion
  - Was awarded Nobel prize in physiology and medicine in 1930
- George Washington Crile, Jan Jansky, Dr. William Stewart Halsted all credited with additional discoveries leading to the modern process of blood transfusions.
So what’s the problem?
Adverse immune mediated reactions

- Different blood types result in different circulating antibodies in serum
- Mixing of incompatible blood types results in severe or possibly fatal immune mediated reaction
- The indirect coombs test identifies antibodies present in recipient serum that could potentially react with donor blood
  - Step 1: Washed RBCs incubated with known human serum → antibodies in serum bind to antigens on RBCs
  - Step 2: Washed RBCs incubated with antihuman globulin
    - If antibodies bound to surface antigen in step 1, RBCs will agglutinate, resulting in positive Coombs test
Adverse immune mediated reactions
So who gets what?

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Donate Blood To</th>
<th>Receive Blood From</th>
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<tbody>
<tr>
<td>A+</td>
<td>A+ AB+</td>
<td>A+ A- O+ O-</td>
</tr>
<tr>
<td>O+</td>
<td>O+ A+ B+ AB+</td>
<td>O+ O-</td>
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<tr>
<td>B+</td>
<td>B+ AB+</td>
<td>B+ B- O+ O-</td>
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<tr>
<td>AB+</td>
<td>AB+</td>
<td>Everyone</td>
</tr>
<tr>
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<td>AB+ AB-</td>
<td>AB- A- B- O-</td>
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</tbody>
</table>
Many types of transfusion reactions

- **Most common reactions**
  - Febrile non-hemolytic reactions
  - Chill-rigor reactions

- **Most serious reactions**
  - Transfusion-associated circulatory overload (TACO)
  - Transfusion-associated acute lung injury (TRALI)
Common Reactions
Febrile non-hemolytic reactions

- **Potential causes**
  - Antibodies against WBC HLA in otherwise compatible donor blood
  - Cytokines released from WBC in stored platelet concentrates

- **Clinical presentation**
  - Temperature increase greater than or equal to 1 degree C
  - Chills
  - Headache
  - Back pain
    - Fevers and chills are also associated with more severe hemolytic reactions, so caution advised if these symptoms develop
  - Most often successfully treated with tylenol/benadryl
    - Future transfusion should be pretreated with tylenol
    - If multiple transfusion reactions occur, leukoreduced blood products should be used.
**Allergic reactions**

- Commonly caused by unknown component in donor plasma or potentially antibodies from allergic donor
- Mild urticaria, edema, dizziness, headache with associated fever
  - Occasionally dyspnea, wheezing, incontinence; indicating generalized smooth muscle spasm
  - Anaphylaxis possible, more likely in IgA-deficient recipient
- Pretreatment protocol for patients with history of allergic reactions
  - 50mg PO/IV benadryl prior to transfusion
Treatment for an allergic reaction

- **STOP TRANSFUSION**
  - **Mild allergic reaction (urticaria/itching)**
    - Treat with 50mg IV/PO benadryl
    - If symptoms resolve, transfusion can be continued
  - **Moderate allergic reaction (generalized urticaria/bronchospasm)**
    - IV hydrocortisone 100-200mg
    - Do not continue transfusion
  - **Severe allergic reaction (anaphylaxis)**
    - Above treatments along with epinephrine and investigation from blood bank
Severe Reactions
Transfusion Associated Circulatory Overload

- Form of pulmonary edema caused by volume excess and circulatory overload
  - Directly related to amount of blood product transfused, therefore, more likely to occur with FFP than with cryoprecipitate
  - OR for TACO
    - 2-4 units; OR 2.0
    - 4-9 units; OR 3.10
    - Greater than 9 units; OR 3.55
- More common in patient that receive high volume of products over short period of time, or those with underlying cardiovascular or renal disease
- Less common than urticaria and nonhemolytic febrile transfusion reactions, more common than anaphylaxis, TRALI, and AHTR
Transfusion Associated Circulatory Overload

- **Common signs/symptoms**
  - All patients with respiratory distress or hypertension within 6 hours of receiving transfusion
  - Symptoms: Dyspnea or orthopnea, especially in the setting of positive fluid balance
  - Patient commonly report headache, and seizures have been reported
  - Signs: hypoxia, hypertension, tachycardia, wide pulse pressure, JVD, S3, pulmonary rales/wheezing

- **Evaluation**
  - R/o PE, cardiomyopathy, valvular disease and arrhythmia

- **Treatment**
  - O2 supplementation
  - Diuresis
  - Ventilatory support
  - Communication with blood bank regarding treatment options
Transfusion Associated Circulatory Overload

- 2 main strategies for prevention
  - Following appropriate transfusion threshold
  - Transfusing appropriate number of units
    - Transfuse 1 unit and waiting to evaluate patient response prior to adding additional units in a patient not actively bleeding
    - Limit of 2 transfusions/day in patients not actively bleeding
    - Avoid overly rapid transfusion, reduce total volume of transfusion products
      - Transfusion center may be able to reduce the volume by spinning down RBC and removing preservatives immediately prior to transfusion
  - Diuresis
    - Typically pre-transfusion, but can also be given during and after transfusion.
Transfusion Related Acute Lung Injury

- Rare, but potentially fatal complication of blood product transfusion
- Definition: new acute lung injury/ARDS occurring during or within 6 hours of transfusion of blood products
  - Historically, plasma concentrates and apheresis platelet concentrates were most likely to cause TRALI reaction
  - 1/5000 units of transfused blood products
    - True incidence unknown
- Leading cause of transfusion related mortality in the US
  - Mortality ranges from 5-58% depending on patient population
Transfusion Related Acute Lung Injury

- Pathogenesis - 2 hit theory
- Neutrophil sequestration and priming in the lung microvasculature
  - Programs neutrophils to respond to otherwise weak or innocuous stimulant
- Neutrophil activation
  - Activation causes release of cytokines and other cytotoxic substances that damage pulmonary capillary endothelium -> inflammatory pulmonary edema
    - Antibodies in blood component against recipient antigen (immune TRALI)
    - Bioactive lipids (BRM) able to active neutrophils (non-immune TRALI)
Transfusion Related Acute Lung Injury

- Clinical presentation
  - Hypoxemia
  - Pulmonary infiltrates on CXR (normal cardiac silhouette)
  - Pink, frothy sputum
  - Fever
  - Hypotension
  - Cyanosis

- Occurs during, or within 6 hours of transfusion
  - Symptoms commonly begin within the first 1-2 hours

- Occasionally, transient drop in neutrophil count can be seen
  - Sequestration in lungs
## Diagnostic criteria for transfusion-related acute lung injury (TRALI) and possible TRALI

<table>
<thead>
<tr>
<th>Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)</th>
<th>TRALI</th>
<th>Possible TRALI</th>
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</thead>
<tbody>
<tr>
<td>■ Acute onset (during or within six hours of transfusion)</td>
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</tr>
<tr>
<td>■ Hypoxemia*</td>
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<td></td>
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<tr>
<td>■ Bilateral infiltrates on frontal chest radiograph</td>
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<td></td>
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<tr>
<td>■ No evidence of circulatory overload/left atrial hypertension</td>
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<tr>
<td>■ No pre-existing ALI/ARDS before transfusion</td>
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- **ALI/ARDS risk factor** at time of transfusion

  - Must be **absent**
  - Must be **present**

Same as for TRALI
Transfusion Related Acute Lung Injury

**Diagnosis:**
- When suspected, evaluate patient condition and vital signs
- Determine the extent of hypoxemia
  - Pulse ox vs ABG
- Stat CXR
- Rule out other potential causes of acute decompensation
Transfusion Related Acute Lung Injury

- Treatment
  - STOP transfusion
  - Immediately report to blood bank
    - Blood bank initiates transfusion reaction workup, including CBC, bilirubin, haptoglobin, Coombs, BNP, N-terminal-pro-BNP, HLA antigen typing.
    - Blood bank compiles list of blood products transfused during last 6 hours and reports to blood supplier
    - Blood supplier recalls products from those donors and performs additional testing
  - Correction of hypoxemia
    - Occasionally CPAP or Bi-PAP will suffice, but 70-80% of patients require ET tube with ventilation
Transfusion Related Acute Lung Injury

- **Hemodynamic support**
  - Often present with hypovolemia and hypotension
    - Goal is to maintain adequate end-organ perfusion
    - Achieved with IVF and vasoactive agents
    - Patient with sustained hypoxemia and stable vital signs, diuretics may be indicated

- **Steroid**
  - IV steroids extensively studied in the setting of ARDS with mixed results
  - Efficacy not well established in the setting of TRALI
    - If administered after lung injury established (typically 14 days since onset), may cause harm

- **Investigational strategies**
  - None are approved, but include treatment with HMG-CoA reductase inhibitors, aspirin, alternative blood products
Transfusion Related Acute Lung Injury

● Prognosis
  ○ Hypoxemia typically resolves in 24-48 hours
  ○ Majority of patient will require ICU admission and ventilatory support
  ○ Mortality rate varies greatly depending on which patient population is studied

● Prevention
  ○ Adhering to guidelines for blood product transfusion, especially plasma
  ○ Identifying donors previously implicated in TRALI reactions
  ○ Selecting donors less likely to be alloimmunized to leukocytes
  ○ Testing for anti-HLA antibodies
Take away points

● No transfusion should be considered benign procedure
  ○ All transfusion carries risk that ranges from itching/hives to death

● It is important to counsel patient on risks
  ○ It is a procedure, it needs a consent
  ○ Benefits need to outweigh risks

● All of these potential causes need rapid assessment from a physician
  ○ Once a reaction occurs, patients often decompensate rapidly
  ○ This should not be triaged via phone if at all possible
  ○ Patients need frequent reassessment

● Ask for back up
  ○ There are lots of smart doctors in this hospital, use them to your advantage
  ○ Dr. Palko