Transfusion Reactions (Non-hemolytic)

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Role of Transfusion Medicine

• Assume that an adverse reaction temporally related to a transfusion to be a transfusion reaction until proven otherwise
• Any adverse reaction to blood components should be reported to Blood Bank personnel
• A Blood Bank physician should be consulted for:
  – Clinical evaluation of patients with reactions
  – Laboratory investigation
  – Recommendations for treatment
  – Selection of appropriate blood components for future transfusion
  – Donor lookback, as needed
  – Reporting any death resulting from transfusion to the Food and Drug Administration
  – Reporting certain reactions and errors to NYSDOH

Blood Bank Workup

• Stop the Transfusion and Evaluate the Patient; maintain IV
• Visual Inspection of Returned Unit
  – Discoloration, clots, growth
  – Hemolysis in lines or bag
• Clerical Check: Patient, Labels, Units, Forms
• Post-transfusion Sample
  – Visual Inspection
• Hemoglobinemia
  – ABO type
  – Direct Antiglobulin Test
  – Other immunohematologic tests, as needed

Additional Testing, if needed

• Retyping of Transfused Unit
• Repeat crossmatch
• Repeat Complete Blood Count
  – Check for appropriate increment
• Haptoglobin and LDH
  – Hemolysis
• Urinalysis (hemoglobin, RBC)
  – Hemoglobinuria
• Liver Function Tests (TB, DB)
  – Unconjugated bilirubin elevation
• Brain Natriuretic Peptide
  – Volume overload
• Mast Cell Tryptase
  – Anaphylaxis
• Quantitative IgA and IgG and IgE anti-IgA antibodies
  – IgA deficiency/Anaphylaxis
• HLA-type, anti-HLA antibodies
  – TRALI
• Blood Cultures
  – Bacterial Contamination

Differential Diagnosis

• Acute
  – Immune
    • Acute Hemolytic (AHTR)
    • Febrile Non-hemolytic (FNHTR)
    • Allergic and Anaphylactic
    • Transfusion Related Acute Lung Injury (TRALI)
  – Non-Immune
    • Bacterial contamination
    • Transfusion Associated Circulatory Overload (TACO)
    • Hypotension
    • Non-immune Hemolysis
    • Hypocalcemia
    • Hypothermia
• Delayed
  – Delayed Hemolytic Transfusion Reaction (DHTR)
  – Transfusion Associated Graft Versus Host Disease (TA-GVHD)
  – Post-transfusion Purpura (PTP)

Classification Scheme for Transfusion Reactions

Grading


Likelihood

Febrile Non-hemolytic Transfusion Reactions

• Definition: ↑ temp > 1ºC (1.8ºF)
• Signs & Symptoms:
  – Chills
  – Cold
  – Rigors
  – Associated Symptoms
    • Headache
    • Nausea
    • Vomiting
• Timing: During or up to 1 hour after transfusion
• Not life threatening but can last up to 8 hours
• 0.5% of non-LR units

Evaluation

• Prompt Clinical Evaluation Required
  – r/o hemolytic transfusion reaction, bacterial contamination, TRALI
  – Underlying disease!
• Return Unit and Post-transfusion samples to Blood Bank for work-up
• Evaluate for other causes: underlying disease, drugs, infections

Treatment FNHTR

• Stop Transfusion if not already stopped
• Acetaminophen 325-500 mg
• Diphenhydramine commonly administered, but has no effect on the course of the reaction
• Meperidine for severe rigors

Leading Fatality Categories*

<table>
<thead>
<tr>
<th>Category</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion-Related Acute Lung Injury (TRALI)</td>
<td>20.1%</td>
</tr>
<tr>
<td>ABO and other hemolytic transfusion reactions</td>
<td>13.9%</td>
</tr>
<tr>
<td>Bacterial contaminations</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

*data from FY 2001-2004; less frequent categories include infections, clear or possible non-transfusion causes, and donor deaths
Prevention FNHTR

- Antipyretics
  - If no history/premed unneccesary
  - 1/8 chance of recurrence
- No role for diphenhydramine or steroids
- Meperidine, if severe shaking chills
- Anti-leukocyte antibodies implicated
- Leukocyte Reduction
  - < 5 x 10^6 leukocytes
  - LR filter or washing
  - Will not prevent all reactions

Allergic (Mild)

- Up to 1% of all transfusions
- Signs & Symptoms
  - Pruritus
  - Urticaria
  - Erythema
  - Cutaneous Flushing
  - Laryngeal edema, hoarseness, stridor
  - Bronchocstriction: wheeze, chest tightness, dyspnea
- Associated Symptoms
  - GI distress (pain, diarrhea)
  - Nausea and Vomiting
- Most commonly due to infusion of plasma proteins
- May occur with FNHTR

Differential Diagnosis

- Other hospital allergens
  - Drugs
  - Tape
  - Latex gloves
  - Ethylene oxide sensitivity (e.g. fiber sterilization for dialysis membranes)
- Underlying allergies
  - e.g. peanuts
- If respiratory
  - Transfusion Associated Lung Injury
  - Transfusion Associated Circulatory Overload

Severe Allergic (Anaphylactic) Reactions

- Can include Signs & Symptoms of Mild Allergic Reactions
- Cardiac instability
  - Hypotension and Shock
  - Tachycardia
  - Arrhythmias
  - Cardiac Arrest
- Respiratory
  - Stridor
  - Dyspnea
- Differential
  - TRALI, TACO, AHTR, Bacterial Contamination
  - IgA Deficiency: IgG or IgE anti-IgA antibodies
- 1:20,000 to 1:50,000

Treatment and Prevention

- Mild
  - Stop Transfusion
  - Diphendydramine 50-100 mg
- Severe
  - Stop Transfusion
  - Supportive Care
    - Oxygen, Intubation, maintain IV
    - Trendelenberg
    - Epinephrine, if needed
      - 0.3-0.5 mg (0.3-0.5 ml of 1:1000 solution) q20 minutes SC
    - Diphenhydramine 50-100 mg
    - Aminophylline 6 mg/kg loading dose IV
  - Consider H2 blockers (e.g. cimetidine)
  - Washed red cells
    - If severe or recurent

Bacterial Contamination Presentation

- During phlebotomy, bacteria can enter the component bag
- Usually Dramatic
- Onset is shortly after transfusion or during the transfusion, but can be delayed
- Signs & Symptoms
  - Fever
  - Chills, Rigors
  - Hypotension
  - Nausea and Vomiting
  - Dyspnea
  - Abdominal Cramps
- Clinical Complications
  - Shock
  - Renal failure
  - DIC
  - Death

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Chills, Rigors</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Hypotension*</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Abdominal Cramps</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

*Signs and symptoms of 63 cases of transfusion-transmitted bacterial infection, Blood Transfus Serv, December 1999-March 2000

TABLE 1: Signs and symptoms of 63 cases of transfusion-transmitted bacterial infection, Blood Transfus Serv, December 1999-March 2000

**Signs and symptoms of 63 cases of transfusion-transmitted bacterial infection, Blood Transfus Serv, December 1999-March 2000**
Work-up and Treatment

- Visual Inspection of Unit (Difficult)
  - Discolored
  - Malodorous
  - clotted
- Culture and Gram Stain of Patient Blood
  - Possibly DNA and endotoxin testing
- Culture and Gram Stain of Unit
  - Possibly Endotoxin and DNA testing
- Stop the Transfusion
- Supportive Care
  - Cardiac
  - Respiratory
  - Renal blood flow
- Broad Spectrum Antibiotic Therapy
  - If PRBC then include Pseudomonas coverage
- Recombinant IL and cytokine inhibitors – RUO?

Transfusion Transmitted Bacteremia

<table>
<thead>
<tr>
<th>TABLE 1. Number of units distributed, number of cases, number of fatalities, and estimated rate of transfusion-transmitted bacteremia by type of blood component, United States, January 1, 1998 through December 31, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Component</td>
</tr>
<tr>
<td>Whole Blood</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Single donor</td>
</tr>
<tr>
<td>Platelets, no pH</td>
</tr>
</tbody>
</table>

Average rate estimated for each component type.

Risk

Prevention

- Donor History Questionnaire
- Antiseptic and Inspection of Phlebotomy Site
- Limiting Storage Time (5 days)
- April 2004 AABB survey (pH and glucose testing)
  - poor sensitivity and poor specificity
- Visual Inspection; Swirling
- Diversion Pouch
- Bacterial Culture
- Endotoxin Testing
- Pathogen Inactivation

Implicated Organisms
Transfusion-Related Acute Lung Injury (TRALI)

- #1 Reported Transfusion-related mortality
- 1/10,000 transfusions
- Up to 20% mortality
- Underrecognized and underreported
- Non-cardiogenic pulmonary edema
- ARDS-like picture
- Signs and Symptoms presenting 1 to 6 hours after the transfusion
- CXR diffuse pulmonary infiltrates
- No elevation in cardiac pressure

Diagnosis

| Table 1: Clinical and Laboratory Features of TRALI |
|---|---|
| Clinical Features | Laboratory Features |
| Acute respiratory distress | Very common |
| Hypotension | Very common |
| Pericardial effusion | Very common |
| Hypoxemia | Very common |
| Fever, rigors, chills | Very common |
| Tachycardia | Common |
| Dyspnea | Severe |
| Hypotension | Life-threatening |
| Leukopenia | Very common |
| Hypocomplementemia | Very common |

NOTE: Adapted with permission.

Treatment and Outcome

- Ventilatory Support
  - O₂ support
  - Intubation usually required
- Circulatory Support
- Steroids
- Diuretics should have no effect
- Most often Self-limited resolving in 48-96 hours
- Death
### TRALI Fatalities

![Graph showing TRALI Fatalities](image)

### Pathophysiology

![Diagram showing Pathophysiology](image)

### Anti-HLA and Anti-PMN antibodies in TRALI

<table>
<thead>
<tr>
<th>Antibodies Detected</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any transaminase antibody detected</td>
<td>59 (94)*</td>
</tr>
<tr>
<td>No antibody detected</td>
<td>29 (47)</td>
</tr>
</tbody>
</table>

*In some cases more than one type of antibody was detected.

### Prevention

- U.K. adopted transfusion of FFP only from male donors
- Markedly decreased the incidence of TRALI compared to historical data (only one year of data)
- Major U.S. Suppliers are changing to all-male plasma
- Specialized Centers of Clinically Oriented Research (SCORR) Trial → to determine incidence and risk factors
- Leukocyte Antibody Prevalence Study (LAPS) → HLA Antibody prevalence and screening strategies

### Lookbacks

- **Post-transfusion Purpura**
  - Profound thrombocytopenia
    - Abrupt onset
    - Often <10 x 10⁹/L
    - 5-10 days after transfusion
  - Purpura
  - Bleeding
  - Possible fever
Posttransfusion Purpura

• Rare (2/100,000 transfusions)
• Similar in concept to DHTR
• Patient makes an alloantibody to a platelet antigen after transfusion; prior transfusion or pregnancy likely
• Destruction of transfused and autologous platelets
• Autologous destruction mechanism not clear
  – Soluble antigen passively attached to autologous platelets?
  – Implicated unit may be any blood component
• Self-limited (< 2 weeks)
• 10-20% mortality

Diagnosis and Treatment

• Identification of platelet alloantibody
• Antigen is not present on recipient’s platelets
• Anti-HPA-1 (PLA1) has been the most commonly reported
• Developed by transfusion or pregnancy
• Platelet survival studies

• Differential Diagnosis
  – ITP
  – TTP
  – HIT (e.g. post cardiac bypass)
  – Drug-induced thrombocytopenia
  – DIC
  – Sepsis

Treatment

• High Dose IVIG
• High Dose Steroids
• Plasmapheresis
  – Category III indication
  – Used when refractory to IVIG and steroids
  – QOD until recovery of platelet count
• Splenectomy
• Platelet Transfusion
  – Not necessary unless active bleeding
  – May be difficult to recruit appropriate donors
  – If antigen negative not available
  – Antigen positive likely to stimulate antibody production
  – Novoseven an option

Prevention

• Unpredictable
• First occurrence not preventable
• PTP should receive platelets that lack the corresponding antigen, but no clear consensus
  – Donor recruitment
  – Donor exhaustion
  – Family Members
• May not recur

Transfusion-Associated Circulatory Overload (TACO)

• All too common occurrence
• Preventable
• Congestive Heart Failure after transfusion
  – Dyspnea, Cynosis, headache
  – Hypoxemia, JVD, Tachycardia, Pulmonary Edema, pedal edema
• DDx: TRALI, Anaphylaxis, Underlying Disease
• Increased Risk in Elderly and Pediatric Patients
• Treat with diuresis and fluid restriction
• Preventable by identifying high risk patients
  – Transfuse over a longer period of time
  – Diuresis
  – Split unit?

Transfusion Associated GVHD (TA-GVHD)

• Immunologically competent lymphocytes transfused into recipient who is immuno-incompetent
• Donor lymphocytes recognize recipient as foreign and initiates an attack against the host
• Graft attacks tissue, but also the bone marrow inducing aplasia (different than GVHD in BMT)
• Fatal in 90%
• 8-10 days post-transfusion
• Marked pancytopenia
• Marked multiorgan involvement esp skin, liver, gut
• Die of infection and bleeding within weeks
### Prevention

- Irradiation of Cellular Components
- Leukoreduction is NOT sufficient
- Irradiation for:
  - Units from blood relatives
  - Allo/Auto HPC Transplant Recipients
  - Intrauterine transfusion
  - Neonates undergoing exchange transfusion or ECMO
  - Hodgkin’s Disease
  - Cellular immune deficiency
  - Solid Organ Transplants?

### Non-immune Hemolysis

- Lysed red cells
- Causes:
  - Increased Transport Temperature
  - Blood Warmers
  - Inadvertent Freezing
  - Small bore needles
  - Bypass pumps
  - Osmotic hemolysis (infusion into same line)
  - Bacterial Contamination
- Possible underlying disease: intrinsic red cell defect
- Consequences:
  - Hypotension, shock
  - Renal failure
  - Hemoglobinemia, hemoglobinuria
  - Hyperkalemia

### Hypotension

- Flushing, hypotension
- ACE Inhibitor + Leukoreduction Filter (Bedside LR)
- ACE Inhibitor + negative charged apheresis kit
- Inhibited metabolism of bradykinins
- Rule out hemolysis
- Stop ACE or hold prior to procedure

### Massive Transfusion/Apheresis

- Electrolytes
  - Hyperkalemia/Hypokalemia
    - ATP-ase become active with rewarming and K+ goes decreases
    - May be a concern for neonates, but fresh units should be fine (0.5 mEq/unit)
  - Hypocalcemia (Citrate)
    - Tingling, chills, muscle cramps and fasciculations
    - Depressed cardiac function
  - Massive Transfusion + Liver Disease
  - Apheresis Procedures with FFP, RBC
- Hypothermia
  - Rapid transfusion of blood components
  - Ventricular arrhythmias
  - Impaired hemostasis

### Other Delayed Reactions

- Iron Overload
  - 200 mg iron per RBC unit
- Alloimmunization
  - Red cell antigens
    - 1-2% per red cell unit
  - Platelet specific antigens
  - HLA antigens
  - Neutrophil specific antigens
- Immunomodulation
  - Improved allograft survival post renal transplant
  - Increased rates of post-operative tumor recurrence