Adverse Effects of Transfusion: Diagnosis & Management of Transfusion Reactions

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Objectives

• Transfusion Reactions
• Transfusion transmitted bacterial infection
• Non-immune Complications of Transfusion
  – TA-GVHD
  – Iron Overload
• Hemovigilance
• Cases
# Transfusion Reactions (TR)

<table>
<thead>
<tr>
<th>Presenting <em>with</em> Fever</th>
<th>Presenting <em>without</em> Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td><strong>Delayed</strong></td>
</tr>
<tr>
<td>- Acute hemolytic TR</td>
<td>- Delayed hemolytic TR</td>
</tr>
<tr>
<td>- Febrile non-hemolytic TR</td>
<td>- Transfusion associated-graft versus host disease (TA-GVHD)</td>
</tr>
<tr>
<td>- Transfusion-transmitted infection</td>
<td></td>
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<tr>
<td>- Transfusion related acute lung injury (TRALI)</td>
<td></td>
</tr>
<tr>
<td><strong>Delayed</strong></td>
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</tr>
<tr>
<td>- Delayed hemolytic TR</td>
<td>- Delayed serologic transfusion reaction</td>
</tr>
<tr>
<td>- Transfusion associated-graft versus host disease (TA-GVHD)</td>
<td>- Post transfusion purpura</td>
</tr>
</tbody>
</table>

**Presenting *without* Fever**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic TR</td>
<td>Delayed serologic transfusion reaction</td>
</tr>
<tr>
<td>Hypotensive TR</td>
<td></td>
</tr>
<tr>
<td>Transfusion associated circulatory overload (TACO)</td>
<td>Post transfusion purpura</td>
</tr>
<tr>
<td>Transfusion associated dyspnea</td>
<td></td>
</tr>
</tbody>
</table>
## Incidence of TR

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>Febrile Non-Hemolytic Transfusion Reaction</td>
<td>1 in 330 RBC units</td>
</tr>
<tr>
<td></td>
<td>1 in 20 Platelet units</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>1-3 in 100 (urticaria)</td>
</tr>
<tr>
<td></td>
<td>1 in 50,000 (anaphylaxis)</td>
</tr>
<tr>
<td>Circulatory Overload</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Transfusion-Related Acute Lung Injury (TRALI)</td>
<td>1 in 5000</td>
</tr>
<tr>
<td>Acute Hemolytic Transfusion Reaction</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Delayed Hemolytic Transfusion Reaction</td>
<td>1 in 1900</td>
</tr>
<tr>
<td>Transfusion Associated Graft vs Host Disease</td>
<td>1 in 1,000,000</td>
</tr>
</tbody>
</table>

Management of a Suspected TR

- Assume all symptoms are signs of an acute hemolytic TR
- Stop the infusion, notify MD and BB
- Keep line open with IVF (0.9% saline)
- Monitor vital signs
- Initiate a laboratory investigation of a suspected HTR
Laboratory Investigation
Hemolytic Transfusion Reactions (HTR)
Diagnosis of HTRs
Causes of HTRs

• Administration of incompatible blood
  – Majority are due to ABO incompatible units erroneously released
  – Failure to detect a potential incompatibility → DHTRs
  – Deliberate, physician-guided use of an incompatible component
Differential Diagnosis

- AHTR
- DHTR
- Autoimmune hemolytic anemia
- Cold hemagglutinin disease
- Nonimmune hemolysis
- Congenital hemolytic anemia
- Hemoglobinopathies
- Drug induced hemolysis
- Microangiopathic hemolytic anemia
- Bleeding
### Treatment and Prevention

- Minimal symptoms are best managed by careful observation
- Severe reactions require early vigorous intervention

<table>
<thead>
<tr>
<th>Indication</th>
<th>Intervention</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prevent renal impairment</td>
<td>• Hydration</td>
<td>• NS</td>
</tr>
<tr>
<td>• Maintain urine output &gt; 100mL/hr and pH &gt;7.5</td>
<td>• Alkalinization</td>
<td>• Sodium Bicarb in 5% Dextrose</td>
</tr>
<tr>
<td>• Prevent renal impairment</td>
<td>• Diuresis</td>
<td>• Mannitol</td>
</tr>
<tr>
<td>• Increase renal blood flow</td>
<td>• Vasodililation</td>
<td>• Furosemide</td>
</tr>
<tr>
<td>• Treat DIC</td>
<td>• Anticoagulation</td>
<td>• Heparin</td>
</tr>
<tr>
<td>• Decrease load of incompatible RBCs</td>
<td>• Red cell exchange</td>
<td>• Exchange of one red cell mass</td>
</tr>
<tr>
<td>• Hemorrhagic complications of DIC</td>
<td>• Transfuse plasma or platelets prn</td>
<td>• Plasma 1-15mL/kg</td>
</tr>
<tr>
<td>• Prevent extravascular hemolysis</td>
<td>• IVIG</td>
<td>• One unit apheresis plts</td>
</tr>
</tbody>
</table>

Adapted from Principle’s of Transfusion Medicine Rossi et al.
Febrile Non-hemolytic TRs

• Commonly defined as an increase of body temperature by 1°C during or within 4 hours of transfusion

• Shaking chills without an elevation in body temperature can also be classified as FNHTRs if temporally related to transfusion and no other cause identified
Complications of FNHTRs

- Rarely patients may develop severe symptoms
- Fever increase $O_2$ demand
Pathophysiology

- FNHTR seems to be part of a systemic immune inflammatory response in patient’s provoked by transfusion
- Currently, 2 accepted theories
• Common pathway
  – Increase in circulating pyrogens
  – Newer models suggest the role of prostaglandins in the CNS
Treatment

• Antipyretics
• Unless signs of an allergic reaction are present, antihistamines are NOT indicated
Prevention

- Premedication with acetaminophen if a history of recurrent FNHTRs
- Steroids
- Reduce the rate of infusion
- Leukoreduction
Allergic TRs

• An immediate hypersensitivity reaction due to the interaction of an allergen with preformed antibodies
• Classified as mild or severe based on the symptoms
Anaphylactic and Anaphylactoid Reactions

• Serious and potentially life threatening
• Rapid onset
• Anaphylaic reactions are differentiated based on their systemic nature and severity
• Affect multiple systems
• Symptoms:
Etiology

- Recipient preformed IgE interacts with an allergen present in the donor plasma.
- PAF induces production of NO which is thought to be the underlying cause of the hypotension and cardiovascular collapse seen during anaphylaxis.
- Rare reports of preformed IgE antibodies in the donor reacting with the antigen in the recipient.
• Anaphylactoid reactions
• Anaphylactic and anaphylactoid reactions have also been attributed to patients with deficiencies of other plasma proteins such as haptoglobin, VWF, or complement components
Diagnosis

• Clinical manifestations

• Serologic BB investigations are usually unrevealing

• Severe reactions
  – Serum β-tryptase or histamine levels
  – Measure IgA levels

• All allergic reactions should be reported to the blood bank
Treatment

• Mild symptoms
  – First-generation H1-blocking antihistamines (Benadryl)
  – Newer second generation antihistamines (loratadine, cetirizine, fexofenadine)
  – H2 blockers (ranitidine, cimetidine) can be added and speed the resolution of symptoms
  – Can resume transfusion after 30 minutes if complete resolution of symptoms has occurred
Treatment

• Anaphylaxis
  – Once clinically evident $\rightarrow$ epinephrine
  – IV crystalloid or colloid for pressure support
  – O2 for respiratory distress
  – Intubation for laryngeal edema/stridor
  – Nebulizers for wheezing
  – Antihistamines for urticaria, angioedema and GI symptoms
  – Glucocorticoids for the late-phase inflammatory response
Prevention

• IgA deficient patients
• Platelet Additive Solution (PAS)
• Washed cellular products
Transfusion-Associated Circulatory Overload (TACO)

- Cardiac insufficiency, renal impairment, or expanded blood volumes
- Rapid infusion of blood increases the risk of TACO
- Symptoms: dyspnea, tachycardia, acute hypertension, and pulmonary edema, right or left sided heart failure
- Diagnosis can be difficult
  - BNP
  - Response to diuretics
- Treatment
  - Diuretics
- Prevention
  - 2-4 mL/kg/hr
  - Diuretics
  - Split units
Hypotensive TR

• Drop in blood pressure occurring during or with in an hour of cessation of transfusion
• Symptoms not accounted for by a more specific TR
• Secondary to the infusion of bradykinin to patients with decreased ACE activity
• Reported in patients receiving bed-side leukocyte reduced platelets and taking ACE inhibitors
Symptoms

• Hypotension
  – Adults: > 30 mmHg drop in systolic BP AND systolic < 80 mmHg
  – Infants and children: >25 mmHg drop in systolic BP AND systolic <90 mmHg
  – Neonates: >25 mmHg drop in systolic BP from baseline

• Responds rapidly to cessation of transfusion and supportive treatment

• May have flushing, dyspnea, or abdominal cramps
Prevention

• Pre-storage leukoreduction
  – Bradykinin is broken down rapidly in the stored unit

• Temporary discontinuation of ACE inhibitor
Post Transfusion Purpura

- Thrombocytopenia arising 5-12 days after transfusion of cellular blood components
- 85-95% of cases are women
- Incidence 1:24,000
- Pt previously sensitized via pregnancy or transfusion
Pathogenesis

• Despite the presence of platelet specific alloantibodies, pathogenesis remains elusive
• Currently accepted hypothesis
Treatment

• IVIG
• 90% response rate
• >100,000 platelets/μL in average 4 days
Bacterial Contamination of Blood Products

• Bacterial contamination of blood components is often overlooked problem
• Recent public attention has focused on transfusion-transmitted viral infections
• Bacterial contamination has emerged as the leading cause of transfusion-transmitted disease
• The FDA, AABB and CAP have instituted requirements to detect bacterial contamination of platelet products
Bacterial Contamination of Blood Products

• Clinical Presentation:
  – Range from asymptomatic to mild fever to acute sepsis and death

• Contamination of components
  – RBC: rare event, risk of death estimated 0.13/million
  – Plasma and Cryo
Bacterial Contamination of Platelet Products

- Platelets are stored at room temperature (20-24°C)
- Approximately 1 in 1,000 to 3,000 units are contaminated
- Septic transfusion rate is 1 in 25,000
Strategies to Reduce the Risk of Posttransfusion Sepsis

• Bacterial Avoidance
  – Donor screening
  – Skin preparation
  – Diversion

• Bacterial Detection
Pathogen Inactivation (PI)

• Development for new tests take on average 1 year after the pathogen has been discovered and described
• PI represent a proactive approach
• Additional safety measure
Non-immune Complications of Transfusion

- Complications of massive transfusion
- Circulatory overload
- FNHTR and allergic TRs
• Non-immune hemolysis
  – Rare
  – Physical or chemical destruction of the cells
    • Heating
    • Freezing
    • Hemolytic drug or solution added to the product
    • Mechanical hemolysis
Transfusion-Associated Graft-vs-Host Disease (TA-GVHD)

- Donor T cells, responding to proteins on host cells, proliferate and target host organs
- Mortality is >90%; Incidence-unknown
- Onset of symptoms is approximately 10 days (2-30)
- Immunocompromised patients are at highest risk
Pathophysiology

• Three requirements
Patients at Risk for GVHD

- **Neonates**
  - Intrauterine transfusion (IUT)
  - Postnatal transfusion in recipients of IUT
  - Very low-birthweight premature neonates
  - Neonatal alloimmune thrombocytopenia

- **Congenital Immunodeficiency**
  - Severe combined immunodeficiency
  - Wiskott-Aldrich syndrome
  - DiGeorge syndrome
  - Other T-cell defects

- **Malignancies and Immunosuppression Caused by Treatment**
  - Leukemia and lymphoma
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Other solid tumors

- **Purine Analog Therapy**
  - Fludarabine

- **Hematopoietic Cell Transplantation**
  - Allogeneic
  - Autologous
  - Syngeneic

- **Solid-Organ Transplant**
  - Lung
  - Liver
  - Heart
  - Kidney
  - Pancreas

- **Surgery**
  - Cardiac surgery
  - Extracorporeal membrane oxygenation

*Adapted from Rossi et al.*
GVHD in Immunocompetent Patients

- Transfusion from a donor that is HLA homologous to the recipient
- Surgery
- Fresh Blood
## Clinical Presentation

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>HSCT GVHD</th>
<th>TA-GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Onset</td>
<td>23 days (12-100 days)</td>
<td>10 days (2-30 days)</td>
</tr>
<tr>
<td>Fever</td>
<td>Often</td>
<td>Usually</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>Rare</td>
<td>Almost always</td>
</tr>
<tr>
<td>Occurrence</td>
<td>25-50%</td>
<td>Rare</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>35-50%</td>
<td>Rare</td>
</tr>
<tr>
<td>Mortality</td>
<td>10-25%</td>
<td>90-100%</td>
</tr>
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Adapted from Rossi et al
Treatment

- Poor prognosis
- Steroids
- Antithymocyte globulin (ATG)
- Extracorporeal photopheresis
Prevention

• 25 Gy gamma irradiation reliably inactivates donor lymphocytes
• Does not damage platelets or granulocytes
• Irradiation
• Pathogen Inactivation
Iron Overload

• Tissue iron overload results in patients who receive regular red cell transfusions
• Initial deposition in liver and reticuloendothelial system
• Starting chronic transfusion later in life mitigates the effects to some extent
Transfusion Associated Iron Burden

- Each unit of red cells contains 200-250 mg of iron
- Body can excrete 1-2 mg/day
Management of Iron Overload

- Chelating agents
- Compliance is the main determinant in the survival of patients
“Hemovigilance”

- Term has become widely used over the past 10 years
- Systematic surveillance of adverse transfusion reactions and events, encompassing the whole transfusion chain and aimed at improving safety of the transfusion process, from donor to recipient, “vein to vein”
- This data along with the clinical assessment of transfused patients provides critical information
- “Biovigilance”
Hemovigilance

• Ability to collect data AND use it to make recommendations that improve patient safety
• Four core concepts:
  – Enhance safety by learning from failures
  – Reporting is only of value when it leads to constructive response
  – Reporting must be safe
  – Meaningful analysis, learning and distribution of lessons learned requires expertise and other human and financial resources
Hemovigilance in the US

• 2010 Biovigilance Component of the National Healthcare and Safety Network (NHSN)
• Participating facilities voluntarily report all transfusion-associated adverse events using a web based tool
• Reactions are classified using standard criteria set forth in the NHSN manual
Questions?