Objectives

To develop an approach to the management of acute (within 24h) transfusion reactions

To discuss the most common transfusion related reactions categorized according to

Fever
Dyspnea
Allergy
# Frequency of Transfusion Reactions: NOT UNCOMMON

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNHTR</td>
<td>1/20 platelet pools, 1/300 RBC</td>
</tr>
<tr>
<td>Hives</td>
<td>1/100</td>
</tr>
<tr>
<td>TACO</td>
<td>1/700</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>1/1000-10,000 platelet pools, 1/50,000 RBC</td>
</tr>
<tr>
<td>TRALI</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1/40,000</td>
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</tbody>
</table>
FEVER
Approach to Acute Transfusion Reactions

For All Acute Reactions

1. **STOP** the Transfusion
2. Check patient ID with ID on component
3. Report to the Transfusion Medicine Laboratory
4. Return the unit
Case 1

41 year old male with lymphoma receiving chemotherapy, hemoglobin 60 g/L, neutrophil count 1.5 x 10^9/L

Transfused 2 U RBCs

4 hours later, fever 40°C, chills, rigors

Hemoglobin 70 g/L
The most likely diagnosis is

- Acute hemolytic transfusion reaction
- Hyperhemolytic transfusion reaction
- Delayed hemolytic transfusion reaction
- Bacterial sepsis secondary to transfusion
Laboratory Tests for Acute Hemolytic Transfusion Reactions: Show the Incompatibility

To show an incompatibility between donor and recipient

Direct antiglobulin test (DAT) and Indirect antiglobulin test (IAT)

Group and screen

Panch SR et al, NEJM 2019:381:150
Laboratory tests for acute hemolytic transfusion reactions: Show the effects of the incompatibility

To determine the effects of the incompatibility, red cell destruction

- CBC (degree of anemia), peripheral smear (spherocytes, schistocytes)
- Hemolytic screen
  - LDH, bilirubin, haptoglobin, reticulocytes
- Coagulation screen (DIC)
- Creatinine
Hemolytic parameters with acute intravascular hemolysis

Time (hours)

- plasma hemoglobin
- urine hemoglobin
- haptoglobin
- serum bilirubin
Etiologies of hemolytic transfusion reactions

IMMUNE CAUSES

ABO incompatible hemolytic transfusion reaction

Transfusion error

Other red cell antigens: Kell, Duffy, Kidd

Emergent use of uncrossmatched RBCs

NON-IMMUNE CAUSES

Osmotic stress — cryopreserved cells inappropriately washed

Thermal

Hypotonic solution

Conditions exacerbated by transfusion:
Autoimmune hemolytic anemia and drug induced anemia

Panch SR et al. NEJM 2019:380:150
Outcome of acute intravascular hemolysis secondary to ABO incompatibility

<10% are fatal

75% of all fatal hemolytic transfusion reactions are secondary to ABO

Dependant on the volume of blood

Most fatalities occur with ≥ 200 ml

Prevention

CSTM standards requires to G&S prior to transfusion
Management summary of suspected hemolytic transfusion reactions

Maintain urine output-crystalloids ± diuretics
100 mL/hour for approximately 24 hour to increase renal clearance, dialysis may be necessary
Hyperhemolysis leads to an acute reduction in Hb < pretransfusion Hb

Reticulocytopenia

May occur within 7 days: DAT may not be positive

After 7 days, DAT may be possible

A medical emergency as may be life threatening

Occurs in 1-19% of sickle cell disease, also other diseases

Further transfusion will exacerbate the hyperhemolysis

IVIG, corticosteroids, erythropoietin,

Eculizumab, rituxan are potential interventions

Case 2

18 year old female with AML admitted with febrile neutropenia

Treated with Piperacillin and gentamycin

3 days following admission she receives 1 adult unit of platelets for a platelet count of 20 x10⁹/L

Immediately following transfusion, has a fever of 39°C and rigors

What is the likely diagnosis?
What is the likely diagnosis?

Sepsis secondary to platelet transfusion

Sepsis

Acute hemolytic transfusion reaction

Unclear presently
Bacteria in blood components may be from

Phlebotomy
  Skin disinfection, donor skin plug

Donor bacteremia

Contamination from the environment
Outcome of bacterially contaminated transfusion

Immunosuppressed and older individuals with poor nutritional status are more susceptible to poorer outcomes

3-year-old girl with AML- platelet transfusion before a CT scan–guided drainage of pleural fluid
Treated with Meropenem
Within minutes of completing the transfusion-febrile, confused, and hypotensive
Died of multisystem organ failure 21 hours after transfusion
The more common organisms causing bacterial sepsis...

<table>
<thead>
<tr>
<th>Product</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells</td>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas spp</td>
</tr>
<tr>
<td></td>
<td>Serratia spp</td>
</tr>
<tr>
<td>Platelets</td>
<td>Staphylococcus aureas and epidermidis</td>
</tr>
<tr>
<td></td>
<td>Propionibacterium acnes</td>
</tr>
<tr>
<td></td>
<td>Bacillus cereus</td>
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Management of bacterial contamination/sepsis

Supportive care - maintain IV access and infuse saline

Culture everything

Broad spectrum antibiotics

Do not wait for cultures to start antibiotics
Pathogen inactivation reduces bacterial contamination in addition to culture of blood component

Photodynamic or photochemical method to the reduce viruses, bacteria, and protozoa

Mirasol system uses riboflavin and UV light to introduce irreparable lesions into nucleic acids inhibiting pathogens and leucocyte replication
Febrile non Hemolytic Transfusion Reaction is a Diagnosis of Exclusion

Type and screen: compatibility

DAT results: negative

Gram stain: negative

Culture: negative

CBC: unchanged
Febrile non Hemolytic Transfusion Reactions

Fever usually within 4 hours: >1º C & > 38º

Symptoms may occur without fever and include

- Rigors, pain, headache, nausea, vomiting
- Hypertension
- Tachycardia
- Diarrhea
- Cough
- Anxiety
Febrile non hemolytic transfusion reactions are mediated by

Antileukocyte antibodies present in recipient plasma
Antileukocyte antibodies in recipients interact with residual donor WBCs to resulting in activation and release of mediators of fever and inflammation, e.g. TNF-α, IL-1β, and IL-6 (cause of FNHTR secondary to red cells)

And/or biologic response modifiers that accumulate in blood products during storage e.g. release of cytokines, chemokines, and byproducts of the complement cascade during storage (cause of FNHTR from platelets)
Summary: Management of Fever Secondary to Transfusion

**Definition**  
>1⁰ C increase in temperature and > 38⁰ during or up to 4 hours following transfusion

- Stop the transfusion
- Check the ID

- Hypotension/shock, tachycardia, rigors/chills, dyspnea, back/chest pain, hemoglobinuria/oliguria, bleeding from IV sites, nausea/vomiting

- **Yes**
  - Do not restart: Acute Hemolytic Transfusion Reaction, Bacterial contamination

- **NO**
  - Acetaminophen, Re-infuse cautiously
  - Febrile Non Hemolytic Transfusion Reaction

Report
DYSPNEA
Case scenario

40 year old male with AML, creatinine 150 µmol/L

Receives 4 units of plasma for an INR of 1.6 prior to a bone marrow biopsy

Following the transfusion acutely dyspneic, 10 mmg Hg drop in systolic blood pressure, chest x-ray shows bilateral chest infiltrates
The most likely diagnosis is

- Transfusion related acute lung injury (TRALI)
- Transfusion associated circulatory overload (TACO)
- Pneumonia
- Transfusion associated anaphylaxis
Transfusion Associated Circulatory Overload (TACO)

“Pulmonary edema following blood transfusion is a frequently encountered and potentially avoidable clinical complication”

Occurs during or within 12 hours of transfusion

Risk factors for TACO:
- chronic renal failure
- a past history of heart failure
- hemorrhagic shock
- number of blood products transfused
- fluid balance
- respiratory disease
Prevention of TACO

AABB Standards for Transfusion Services and Blood Banks (30th edition) requires hospitals to have a policy for issuing blood for those at increased risk for TACO

Identify risks pre transfusion for volume overload

Optimize volume status prior to transfusion

Decrease the infusion rate

Diuretics pretransfusion halfway through or at the end of transfusion
Criteria for Transfusion Related Acute Lung Injury

Acute Lung Injury (ALI)

1. Acute onset
2. Hypoxemia: $\text{SpO}_2 < 90$
3. Bilateral chest infiltrates

$2^\circ$ anti HLA and HNA antibodies in the donor to antigens in the recipient or an inflammatory response
Criteria for Transfusion Related Acute Lung Injury

2. No preexisting ARDS

3. During or within 6 hours of transfusion

4. No temporal relationship to an alternative risk factor for ARDS

5. No left atrial hypertension or if present not causative for hypoxemia
   • If preexisting lung injury, lung injury is stable within last 12 hours
   •* Reverse TRALI cases reported

<table>
<thead>
<tr>
<th>Characteristics to differentiate TRALI and TACO</th>
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<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Frequently reported in hematology and surgical patients</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>All ages, but age &gt; 70 yrs characteristic</td>
</tr>
<tr>
<td><strong>Type of component</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Usually plasma or platelets</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td><strong>Speed of onset</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>During/within 6 hrs of transfusion</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Within 12 hours of transfusion</td>
</tr>
<tr>
<td><strong>Oxygen saturation/ BP/JVP/Temperature</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Reduced/often reduced/normal/raised</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Reduced/often raised/raised/unchanged</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Normal heart size</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Cardiomegaly</td>
</tr>
<tr>
<td><strong>Echo/PCWP/BNP</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Normal/low/normal</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Abnormal/raised/raised</td>
</tr>
<tr>
<td><strong>CBC</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>May have neutropenia followed by neutrophilia</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>No specific changes</td>
</tr>
<tr>
<td><strong>Response to fluids/Lasix</strong></td>
</tr>
<tr>
<td>TRALI</td>
</tr>
<tr>
<td>Improves/Worsens</td>
</tr>
<tr>
<td>TACO</td>
</tr>
<tr>
<td>Worsens/Improves</td>
</tr>
</tbody>
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Treatment of TRALI vs TACO

TRALI: Supportive care

Mild - oxygen

Severe - ventilatory support

Diuretics not recommended

Mortality for TRALI is estimated between 5% - 25%
TACO needs to be differentiated from TRALI

To defer the implicated donor
Antibody mediated TRALI

Male only plasma has reduced TRALI

Solvent detergent plasma may also reduce TRALI
Transfusion Associated Dyspnea

Respiratory distress within 24 hours of transfusion

Does not fulfill criteria for TRALI, TACO, allergy
ALLERGIC REACTIONS
Anaphylaxis secondary to transfusion may be due to

- Anti-IgA in an IgA deficient patient (<0.05mg/dl)
  - 1/300 to 1/500
  - 40-50% will have antibodies

- Haptoglobin deficiency (1/1000 in Asians)

- Passive transfer of IgE

- Antibodies to proteins e.g. haptoglobin

- Transfusing an allergen
  - Incidence higher with plasma containing components
Symptoms suggestive of a severe allergic reaction include:

- Dyspnea
- Hypotension
- Rash >2/3 body
- Tachycardia
- Nausea
- Vomiting

Do not restart the transfusion.

Diphenhydramine/corticosteroids
Transfusion associated hypotension occurs within 15 min of transfusion.

A drop in blood pressure of >30 mmHg

Resolves with discontinuing transfusion within 10 min

Increased bradykinin generation exacerbated with ACE inhibitors

   ACE is a key enzyme in the bradykinin degradation

For patients requiring longterm transfusion-change of antihypertensive should be considered
Summary

Transfusion reactions do not occur uncommonly after transfusion.

Reporting of transfusion reactions assist in identifying the correct diagnosis, and preventative measures.