In the name of god

Acute transfusion reactions

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Introduction

- Acute transfusion reactions range from clinically benign to life-threatening reactions

- Signs and symptoms during or within 24 hours after completion of a transfusion
Life threatening
1. AHTR
2. TRALI
3. TACO
4. Anaphilaxy
5. Sepsis

Non life threatening
1. FNHTR
2. UTR
3. Hypotensive reactions
Frequency of ATR

Common:
1. urticaria
2. FNHTR

Relatively common:
1. TACO
2. TRALI

Relatively rare:
1. Anaphylaxis
2. AHTR
3. sepsis

Very rare:
1. Primary hypotensive reactions
2. Non-immune hemolysis
3. Airembolism
Acute hemolytic transfusion reaction (AHTR)

- Mechanism of RBC destruction
- ABO incompatibility
- Transfusion of plasma-containing products
- Antibodies to most other RBC antigens
Acute hemolytic transfusion reaction (AHTR)

**Time of onset:**

- Typically occur early during the transfusion (a few mL of incompatible blood)
- Approximately 1 in 70,000 per blood product transfused

**Clinical presentation:**

- Classic triad of fever, back pain, and red or brown urine is rarely seen

- Chills, fever, hypotension, hemoglobinuria, renal failure, back pain, DIC
- The serum or urine may be pink due to the presence of free HB
- In a patient under anesthesia or in a coma, oozing from venipuncture sites due to DIC or change in the urine color to red
AHTR : diagnosis

Clinical presentations

Laboratory features:

- Hemoglobinuria, findings of immune hemolysis (Positive DAT), PBS
- ↓ Serum haptoglobin
- ↑ LDH
- ↑ Indirect bilirubin levels
- Testing for DIC if the patient has obvious signs of intravascular hemolysis (pink serum or urine, hypotension) or signs of DIC (PT, PTT, fibrinogen, D-dimer, PLT count)
AHTR: management

Immediately stopping the transfusion

Providing hemodynamic support:

1. Hydration IV (normal saline 10-20 CC/kg)
2. Furosemide (1-2 mg/kg/dose) IV to maintain urine flow (1 CC/kg/h)
3. Dopamine (5 mg/kg/min) for hypotension
4. FFP, platelets, cryoprecipitate for DIC

Contacting the transfusion service

Evaluation for non-immune hemolysis
Febrile non hemolytic transfusion reaction (FNHTR)

Most common of all transfusion reactions (0.1 to 1 %)
More frequent in children than adults
FNHTRs can occur with any products

Causes:

- Cytokines that are generated during the storage of blood components
- Antibodies against class I HLA, PLT or granulocyte antigens
- Platelet-derived CD154 (CD40 ligand)
FNHTR : Clinical presentation

Time of onset: within one to six hours after initiation of a transfusion

Clinical manifestations:

Fever, often a chill, occasionally severe rigors and sometimes mild dyspnea

The temperature increase is typically in the range of 1 to 2°C
A temperature increase of <1°C is not considered clinically significant
An increase of >2°C is more suggestive of an AHTR or septic transfusion reaction
FNHTR : Diagnosis

FNHTRs are diagnosed clinically

Excluding other causes of fever in a patient receiving a transfusion (TRALI, SEPSIS, AHTR)
FNHTR : Management

• Stopping of the transfusion

• Administration of antipyretics (Acetaminophen (10-15 mg/kg/dose orally))

• Evaluation for other causes of fever

• Mepredine for severe chills or rigors
FNHTR : Prevention

- Pre storage leukocyte reduced blood components
- Premedication (acetaminophen) to decrease the incidence of FNHTRs?
- Pre medication with acetaminophen 30-60 min prior to subsequent transfusions in patients with history of FNHTR
- Washed blood components for recurrent FNHTRs despite premedication
Anaphylactic transfusion reactions

Incidence of 1 in 20,000 to 1 in 50,000

IgE-mediated immune reaction

Causes:
1. Transfused product contains a substance to which the recipient is allergic OR contains IgE that reacts with a substance in the recipient
2. Anti-IgA antibodies in patients who are IgA deficient
3. Blood product transfusion in patients with Ahaptoglobinemia who develop anti-haptoglobin antibodies
Anaphylactic transfusion reactions

Products:

RBCs, platelets, granulocytes, or plasma products (FFP, Cryoprecipitate, IVIG)
Clinical presentation and diagnosis of anaphylactic reactions

Time of onset: within a few seconds to a few minutes following initiation of a transfusion

Clinical manifestations:
- shock, hypotension, angioedema, respiratory distress, and/or wheezing

Diagnosis:
- clinically based on the timing of the reaction, rapid progression to potentially life-threatening symptomatology, and rapid response to therapy

The differential diagnosis:
- TRALI, TACO, sepsis (generally not associated with wheezing and angioedema, and they do not resolve rapidly with epinephrine)
Evaluation & treatment

Evaluation:
1. IgA levels as well as anti-IgA (if indicated) on a pre-transfusion sample
2. CXR

Treatment:
1. Immediate cessation of the transfusion
2. Epinephrine
3. Resuscitation of hypotensive patients with intravenous fluids
4. Airway maintenance, oxygenation
5. Vasopressors (dopamine), if necessary
Urticarial transfusion reactions

One of the most common transfusion reactions (1 to 3 percent)

Causes:
A soluble substance in the plasma of the donated blood product (or the recipient) reacts with pre-existing IgE antibodies in the recipient (or the product)

The major difference between allergic reactions and anaphylactic reactions is the degree of reaction
Clinical presentation and diagnosis of urticarial reactions

Time of onset:
During, at the end, or shortly after a transfusion

Clinical manifestations:
Hives or urticaria
No wheezing, angioedema, or hypotension

Diagnosis:
Clinically when a patient develops hives or urticaria without progression to more severe symptoms
Improvement of the urticarial symptoms with stopping the transfusion & administration of diphenhydramine

Evaluation (allergy testing):
For patients who have recurrent urticarial
Management

- Stop transfusion
- Diphenhydramine, orally or IV (1 mg/kg/dose)
- Methylprednisolone IV 1-2 mg/kg/dose (max dose 125 mg)
- If the urticaria wanes and there is no evidence of dyspnea, hypotension, or anaphylaxis, the transfusion may be resumed

Rarely, an urticarial reaction may be the first sign of a more serious reaction. (hypotension or respiratory distress : anaphylaxis)
Prevention

For patients who experience severe or repeated urticarial reactions

1. Premedication with antihistamine 1 h prior to transfusion

2. Consider oral prednisone 1-2 mg/kg/dose Q6 h beginning 24 h before transfusion

3. Concentrating the implicated cells (RBCs or platelets) first by removing plasma

4. Washing the cells if plasma removal does not prevent the urticarial reactions
Transfusion-transmitted bacterial infection (TTBI)

Incidence of blood products contaminations:
Approximately 1 in 2000 for platelets and 1 in 30,000 for RBC (In the United States)

Definition:
Presence of organisms cultured from both the blood product bag and the recipient

Source of organism:
Donor blood, donor skin, the phlebotomist's skin, or environmental contamination during production or packaging

Platelet: higher risk of contamination
Clinical manifestations of TTBI

- **Time of onset:** 30 minutes (range 0 to 5 hours)
- **Fever:** >39ºC (or an increase of >2ºC following transfusion)
- **Rigors**
- **Tachycardia**
- **Rise or fall in systolic blood pressure:** (>30 mmHg)
- **Abdominal pain, back pain, nausea, vomiting, & hypothermia**
- **Variation in presentation of TTBI:** size of the bacterial inoculum, bacterial virulence & the recipient's immune status
Evaluations and treatment

- Stop the transfusion immediately
- Resuscitate the patient
- Blood culture, DAT, plasma-free hemoglobin, repeat crossmatch & typing, UA
- Check for clerical error
- If there is high suspicion for TTBI (fever together with hypotension, shock, or respiratory failure): vancomycin and a broad-spectrum beta-lactam or an aminoglycoside
- Alert the hospital blood bank and microbiology laboratory
- Seal the blood product bag and send to the microbiology lab for Gram stain and culture
- Co-components from the same donation should be quarantined
Prevention

● Donor screening
● Skin preparation
● Sample diversion
● Increasing culture volume
● Preferential use of apheresis
● Reduced storage time
● Leukodepletion
● Bactericidal treatments
● Culture

Molecular techniques for detecting bacterial contamination: more sensitive than older methods
Transfusion related acute lung injury (TRALI)

- Incidence: <0.01 %
- A patient develops hypoxemic respiratory insufficiency during or shortly after transfusion of any blood product

**Cause:**

- **Neutrophil sequestration and priming:** Injury to endothelial cells
- **Neutrophil activation:** activation of recipient neutrophils by a factor in the blood product:
  - Antibodies in the blood component directed against recipient antigens, HLA class II (immune TRALI)
  - Soluble factors such as bioactive lipids that can activate neutrophils (non-immune TRALI)
Risk factors for TRALI

Recipient risk factors

Blood component risk factors:

All plasma containing blood component have been implicated

Plasma components and apheresis platelet concentrates

Donor risk factors: Donor sex
TRALI: Diagnosis

TRALI is a clinical diagnosis

Time of onset: within 6 hours after starting transfusion

Clinical presentation:
- Dyspnea, hypoxemia, fever, non-cardiogenic pulmonary edema, hypotension not responsive to fluid resuscitation and bilateral pulmonary infiltrates

Evaluations:
- Vital signs, pulse oximetry, CXR, ABG (in severe cases)
- HLA- or granulocyte-specific antibodies in donor or recipient plasma strongly suggestive of diagnosis
TRALI : Treatment

TRALI is often self-limited

- Resolution in 48 to 96 hours in most patients with supportive care oxygen supplementation
- Corticosteroids may be of benefit
- Non-invasive respiratory support with continuous positive airway pressure (CPAP) or (BiPAP)
- Endotracheal intubation with invasive mechanical ventilation is often required (approximately 70 to 80 %)
TRALI: Prevention

• Minimization of transfusion

• Deferring donors implicated in a case of TRALI from future platelet apheresis, plasma apheresis, and possibly also whole blood donation

• Most developed countries have adopted a policy of supplying transfusable plasma products (plasma, platelets, and whole blood) exclusively or predominantly from male donors, female donors with no prior pregnancy, or from donors who test negative for HLA-antibodies
Transfusion associated circulatory overload (TACO)

Incidence: <1 percent of transfused patients

Causes:
1. Volume excess or circulatory overload
2. Large volume of a transfused product over a short period of time

Risk factors:
Pre-existing cardiac and renal dysfunction
Positive fluid balance
Larger amount of plasma transfused
Faster blood product infusion rate
TACO : Clinical manifestation

Time of onset:
Respiratory distress or hypertension during or within 12 hour of completing a transfusion

Clinical manifestations:
Mild dyspnea to acute respiratory decompensation
Headache is common
Seizures have been reported

Findings on examination:
Hypoxia and/or hypertension
Tachycardia
wide pulse pressure, and/or jugular venous distension
S3 heart sound
Rales and wheezing
Definitive TACO

New onset or exacerbation of three or more of the following within 12 hours of the end of a transfusion without another explanation:

• Respiratory distress (acute or worsening)
• Evidence of pulmonary edema on examination or radiographs
• Elevated brain natriuretic protein (BNP) or NT-pro BNP
• Other unexplained cardiovascular changes (elevated central venous pressure)
TACO VS TRALI

- TRALI may occur closer in time to the initiation of the transfusion (before significant volume is infused)
- Often associated with hypotension, fever, and transient leukopenia
- TRALI is not associated with an elevated N terminal Pro-BNP (NT Pro-BNP), central venous pressure, or pulmonary artery wedge pressure
Management

**Oxygen:** Supplemental oxygen if $\text{SpO}_2 < 90\%$

**Fluid mobilization:** a key component of management (diuretics)

**Ventilation support:** severe cases of TACO

**Resuming transfusions:**

- TACO is a reaction to the volume of the transfusion

- The four-hour limit for completing the transfusion will have passed by the time
TACO : Prevention

- Avoiding unnecessary transfusion
- Transfusing one unit of red blood cells (RBCs) and waiting to assess the patient's response (in high-risk patients)
- Limiting transfusion of RBCs to 20cc/kg/day in patients who are not actively bleeding
- Avoiding overly rapid transfusion rates (2.0 to 2.5 mL/kg per hour or 1 mL/kg per hour in high risk patients)
- **Diuresis (furosemide):** those already receiving chronic diuretic therapy, those known to require diuresis with previous transfusions, those at high risk of TACO, those who are in heart failure (HF), and those with a history of TACO
Suspected acute transfusion reaction

- STOP transfusion
- Establish/maintain patent IV
- CONFIRM correct product for patient
- ASSESS patient for fever, cardiovascular status, respiratory status, urticaria/angioedema

- No fever
  - Respiratory distress
    - Hypotension
      - TACO suspected
      - Chest radiography, oxygenation status
      - Supportive data:
        - Hypoxia
        - Infiltrate on CXR
        - Diuretic response
        - Hypertension
        - High cardiac filling pressures
        - High NT-proBNP
        - Cardiac history
        - Older age
        - Large infusion volume

- Fever +/- chills
  - Respiratory distress
    - Urticaria/angioedema
      - Bronchospasm
      - Angioedema
      - Hypotension
      - Urticarial or anaphylactic reaction suspected

- Fever/chills
  - Otherwise asymptomatic
    - Hypotension
    - Flank/back pain
    - Bleeding
    - FNHTR suspected
    - DAT (Coombs) test
    - CBC, urine dipstick
    - Supportive data:
      - Lack of any findings associated with AHTR, TRALI, sepsis, or other systemic illness (ie, diagnosis of exclusion)
      - Non-leukoreduced blood products

- Fever +/- chills
  - Hypotension
  - +/- Hypotension
  - FLALI suspected

- Fever +/- chills
  - Hypotension
  - +/– Hypotension

- Fever +/- chills
  - Hypotension
  - +/– Hypotension

- Fever +/- chills
  - Hypotension
  - +/– Hypotension

- Urticaria/pruritus
  - Anaphylactic reactions may have:
    - Wheezing
    - Angioedema
    - Hypotension
    - Low IgA level; anti-IgA
  - Urticarial reactions have urticaria alone
  - Supportive data:
    - Hemoglobinemia
    - Hemoglobinuria
    - Positive DAT
    - Low haptoglobin
    - High LDH; bilirubin
    - Findings of DIC
    - Clerical error discovered
    - More common with platelets
  - Infection may also be related to the patient underlying illness
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