Adverse Transfusion Reactions/ Events

Workshop on Haemovigilance

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Core Topics

1 Haemovigilance

2 Scope of Haemovigilance

3 Adverse Transfusion Reactions

Aim of the Topic

World Health Organization

To provide an overview of the categorization of Transfusion Reactions as a part of Haemovigilance

Learning outcomes

Participants should be able to:

- Understand the type of Transfusion Reactions in recipients

Haemovigilance

World Health Organization

“A set of surveillance procedures, from the collection of blood and its components to the follow up of recipients to collect and assess information on *unexpected* or *undesirable* effects resulting from the therapeutic use of labile blood products and to prevent their occurrence or recurrence”

Scope of Haemovigilance

World Health Organization

Recipient

- Transfusion Reactions (Acute / delayed)
- Transfusion Incidents

Products, Process

- Blood components, Plasma derivatives
- Errors, Near Miss events

Donors

- Complications of blood donation
- Surveillance of infectious disease markers

Adverse Transfusion Reactions

Definition

- Transfusion reaction refers to undesirable, unintended, adverse response to the administration of blood, blood components, or derivatives that are well thought-out to be definitely probable or possibly related to this product.

- About 0.5–3% of all transfusions result in transfusion reaction.

Adverse Transfusion Reactions

Types

- Blood transfusion reactions can be categorized
  - **Infectious**
  - **Non-Infectious**
    - Acute (< 24 hours)
      - Immunological
      - Non Immunological
    - Delayed (> 24 hours)
      - Immunological
      - Non Immunological

Adverse Transfusion Reactions

Infectious Hazards of Transfusion

- Viral Infections
- Bacterial Infection
  - Bacterial Sepsis or contamination
- Protozoal Infections

Adverse Transfusion Reactions

Infectious Hazards of Transfusion

- Historically, transfusion-transmitted infections (TTIs) dominated the transfusion safety agenda.
- Rare in developed countries common in developing and under-developed countries.

Adverse Transfusion Reactions

Characteristics of a Transfusion Transmitted Infectious Agent

- Presence of the agent in one or more of the components of blood
- Propensity for causing asymptomatic (sub-acute) infection in a donor
- Protracted incubation period to the development of symptoms
  - A long-term carrier state of expressed microbial components (e.g. HBsAg in the case of hepatitis B virus)
- The microbial nucleic acid could reactivate to initiate infection in the recipient of a transfusion from an infected donor.

Infectious Hazards of Transfusion

World Health Organization

Viral

- HIV I & II
- HTLV
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis E
- CMV
- West Nile Virus
- HPV B19

Bacterial

- Treponema pallidum
- Gram positive bacteria,
  - Staphylococcus aureus
- Gram negatives,
  - E. coli,
  - Klebsiella spp. and
  - Pseudomonas spp.,

Protozoal

- Plasmodium
- Trypanosoma cruzi

Non Infectious Hazards of Transfusion

ACUTE TRANSFUSION REACTIONS(< 24Hr)

Immune Mediated

- Acute Haemolytic Reactions
- Febrile Non Haemolytic Transfusion Reactions (FNHTRs)
- Severe Allergic or Anaphylactic Reaction
- Severe Allergic Reactions Associated with IgA Deficiency
- Transfusion-related Acute Lung Injury (TRALI)

Non Immune Mediated

- Transfusion-Associated Circulatory Overload (TACO)
- Hypotensive Reactions
- Hypothermia (Rapid infusions)

DELAYED TRANSFUSION REACTIONS(>24Hr)

Immune Mediated

- Delayed Haemolytic Transfusion Reactions (DHTRs)
- Transfusion Associated Graft-versus-host Disease (TA-GVHD)
- Post-Transfusion Purpura (PTP)

Non Immune Mediated

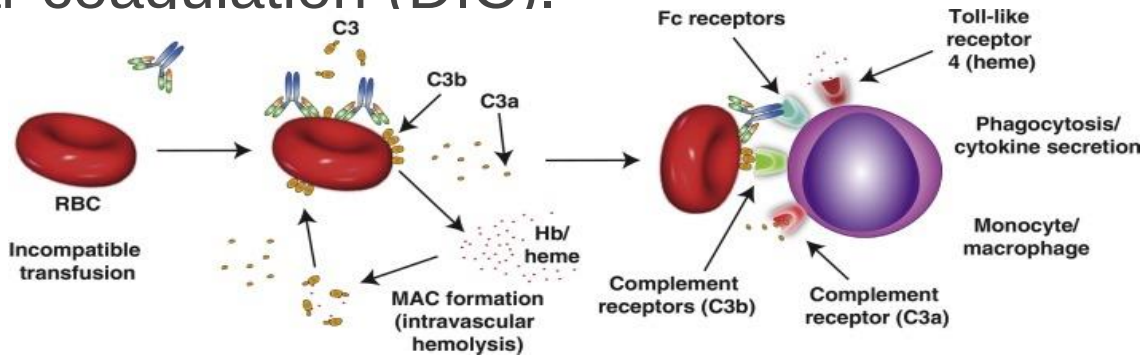
- Iron Overload

G. Clarke| Practical review of acute transfusion reactions| ISBT Science Series (2016) 0, 1–7

Acute Haemolytic Reactions

Definition

- Most serious type of reactions
- Transfusion of ABO-incompatible red cells which react with the patient's anti-A or anti-B antibodies results in Acute Hemolytic Reaction.
- There is rapid destruction of the transfused red cells in the circulation (intravascular haemolysis) and the release of inflammatory cytokines.
- The patient often quickly becomes shocked and may develop acute renal failure and disseminated intravascular coagulation (DIC).



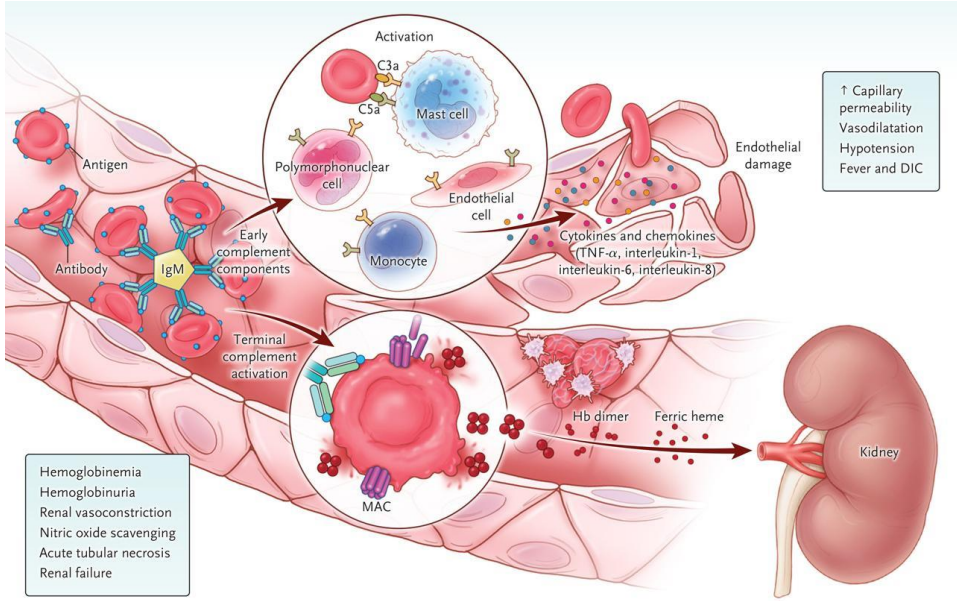
Arthur M.C. et al. Examining the Role of Complement in Predicting, Preventing, and Treating Hemolytic Transfusion Reactions. Transfusion Medicine Reviews, Vol 33, Issue 4, 2019, 217-224,

Acute Haemolytic Reactions

Presentation

- Conscious patients often become very unwell within the first few minutes of transfusion,
  - Complaining of Flushing,
  - Loin and abdominal pain, Nausea, Vomiting, dyspnea, wheezing
  - Hemoglobinuria, hypotension, renal failure, DIC, Shock
  - *‘a feeling of impending doom’*

- If the patient is unconscious or anaesthetised
  - Tachycardia,
  - Hypotension and
  - Bleeding into the skin or needle wounds



Sandhya RP. Hemolytic Transfusion Reaction. N Engl J Med 2019; 381:150-162

Febrile Non Haemolytic Transfusion Reactions (FNHTRs)

Definition

- Feature of fever ≥ 39C oral or equivalent and a change of ≥1C from pretransfusion value, with or without chills, rigors, headache, nausea.
- Usually occurs within 4 hours of transfusion and without any evidence of hemolysis, bacterial contamination or underlying condition.

Jahn Ayodele Olaniyi| Blood Transfusion Reaction 2019| DOI: http://dx.doi.org/10.5772/intechopen.85347

Febrile Non Haemolytic Transfusion Reactions (FNHTRs)

Pathophysiology

- Two possible causes
  1. *Anti-leukocyte antibodies* in recipient
     - More common in multiply transfused patients and multiparous women
  2. *Donor-derived leukocytes*
     - Blood products may liberate cytokines (IL1, IL6, IL8, and TNF) in the course of storage
     - Pre-storage leukoreduction may reduce the accumulation of these biologic mediators and the incidence of febrile, hypotensive transfusion reactions.

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Febrile Non Haemolytic Transfusion Reactions (FNHTRs)

Clinical Presentation

- Fever during or up to 4 hours after transfusion.
- The patient may experience
  - Chills, rigors, nausea and vomiting, and hypotension without fever.
  - Fever (defined as an increase in temperature of 1°C above the patient's baseline temperature, typically to 38°C) with or without chills and/or rigors.
  - Symptoms are self-limited and respond to symptomatic treatment

- Close differentials to FNHTRs include acute haemolytic transfusion reaction and septic transfusion reactions and patients' underlying medical condition.

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Severe Allergic or Anaphylactic Reaction

Mild Allergic Reaction

- Symptoms are confined to
  - Itching (pruritus) and/or skin rash (‘nettle rash’ or hives), no change in vital signs.
  - Mostly with plasma-rich components such as FFP or platelets.
- Symptoms often improve if the transfusion is slowed and an antihistamine (e.g. chlorpheniramine) is administered orally or intravenously.
  - The patient must be monitored closely for development of a more severe reaction, in which case the transfusion must be stopped.
  - Several studies, including randomised controlled trials, have shown no benefit for routine pre-medication with antihistamines or steroids.

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Severe Allergic or Anaphylactic Reaction

Severe Allergic Reaction

- Shock or severe hypotension associated with
  - wheeze (bronchospasm), stridor from laryngeal oedema or swelling of face, limbs or mucous membranes (angioedema) is strongly suggestive of anaphylaxis – an acute, life-threatening emergency.
- Severe allergic and anaphylactic reactions may occur with all blood components but are most commonly reported with plasma-rich components such as platelets or FFP.

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Severe Allergic Reactions Associated with IgA Deficiency

Severe Allergic Reaction

- Only a small minority of patients with IgA deficiency are at risk of developing severe allergic reactions to blood components.
- Those at most risk have severe IgA deficiency (<0.07 g/L), often with anti-IgA antibodies
- There are also reports of patients with deficiency of haptoglobin and various complement components such as C4a (Rogers antigen) or C4b (Chido antigen) developing anaphylactic reactions to platelets

- Jahn Ayodele Olaniyi| Blood Transfusion Reaction 2019| DOI: http://dx.doi.org/10.5772/intechopen.85347
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Severe Allergic Reactions Associated with IgA Deficiency

Severe Allergic Reaction

- In elective situations they should be transfused with blood components from IgA-deficient donors.
- If IgA-deficient components are not available within a clinically relevant timeframe (e.g. acute haemorrhage)
  - **Washed red cells** should be used (washed platelets resuspended in platelet additive solution still have significant amounts of IgA in the plasma).

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Transfusion-related Acute Lung Injury (TRALI)

Definition

- Classical TRALI is caused by antibodies in the donor blood reacting with the patient's neutrophils, monocytes or pulmonary endothelium.
- Inflammatory cells are sequestered in the lungs, causing leakage of plasma into the alveolar spaces *(non-cardiogenic pulmonary oedema)*.
- Most cases present within 2 hours of transfusion (maximum 6 hours) with severe breathlessness and cough productive of frothy pink sputum.
- It is often associated with hypotension (due to loss of plasma volume), fever and rigors and transient peripheral blood neutropenia or monocytopenia.

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Transfusion-related Acute Lung Injury (TRALI)

Definition

- A consensus definition of TRALI is acute lung injury (ALI) defined as
    - Acute onsets (within 6 hours)
    - Hypoxemia ($PaO_2/FiO_2 < 300$ mm of Hg, O_2 saturation < 90% on room air or other clinical evidence),
    - Bilateral pulmonary infiltrates,
    - No evidence of circulatory overload
    - No other associated causes

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Transfusion-related Acute Lung Injury (TRALI)

Pathophysiology

- The development of TRALI, which is a potentially life-threatening reaction, is triggered by
  - Passive transfusion of donor anti-granulocyte antibodies (anti-HLA or anti HNA antibodies), cytokines, biologically active lipids, or other substances into the recipient.
  - These cause acute lung injury with noncardiogenic pulmonary edema.
  - The signs and symptoms comprise dyspnea, hypoxemia, hypotension, fever, and a chest X-ray showing bilateral lung infiltrates with pulmonary edema

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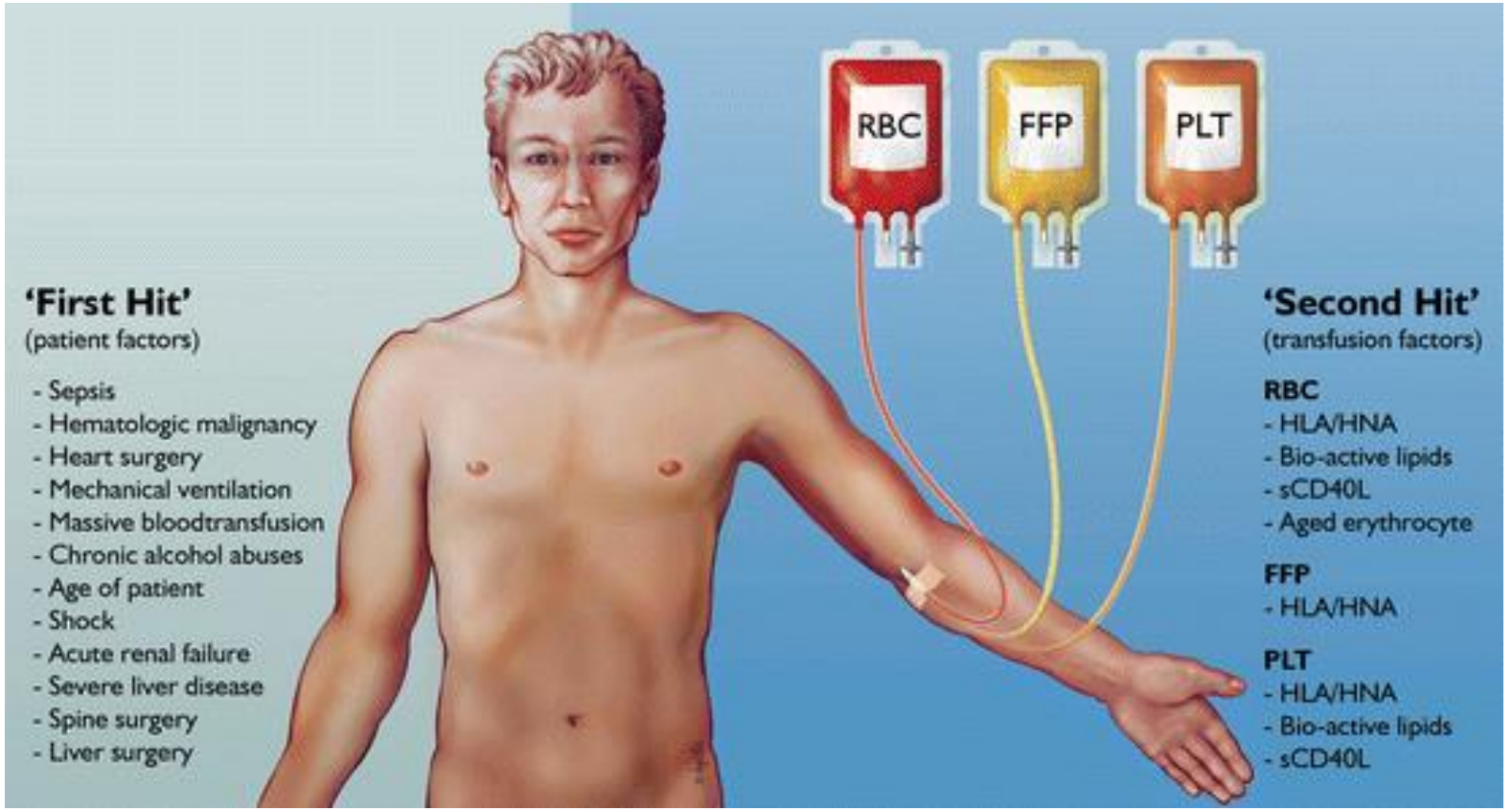
Transfusion-related Acute Lung Injury (TRALI)

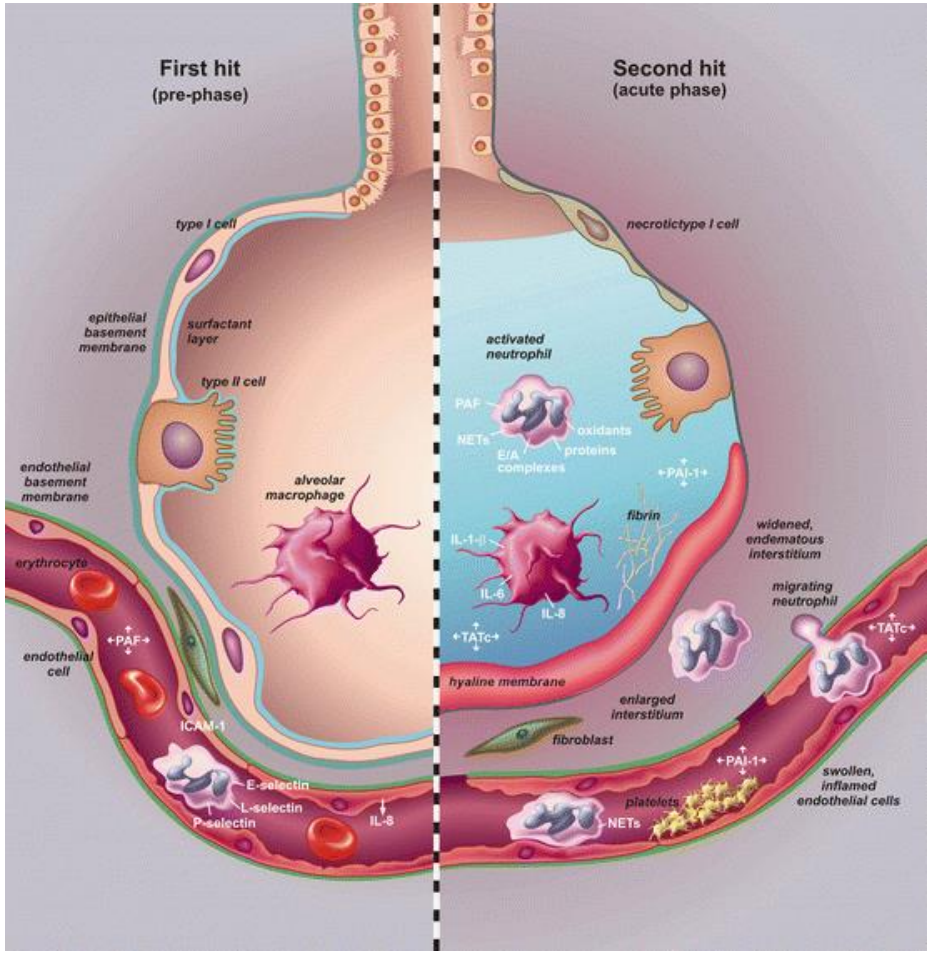
Pathophysiology



Transfusion-related Acute Lung Injury (TRALI)

Pathophysiology

- Mediators of inflammation in the infused blood products (FFP > platelets > RBCs) containing donor anti-granulocyte antibodies (anti-HLA and anti-HNA antibodies) along with cytokines and biologically active lipids activate inflammatory cascade through polymorph-nuclear cells (PMNs) with resultant capillary injury



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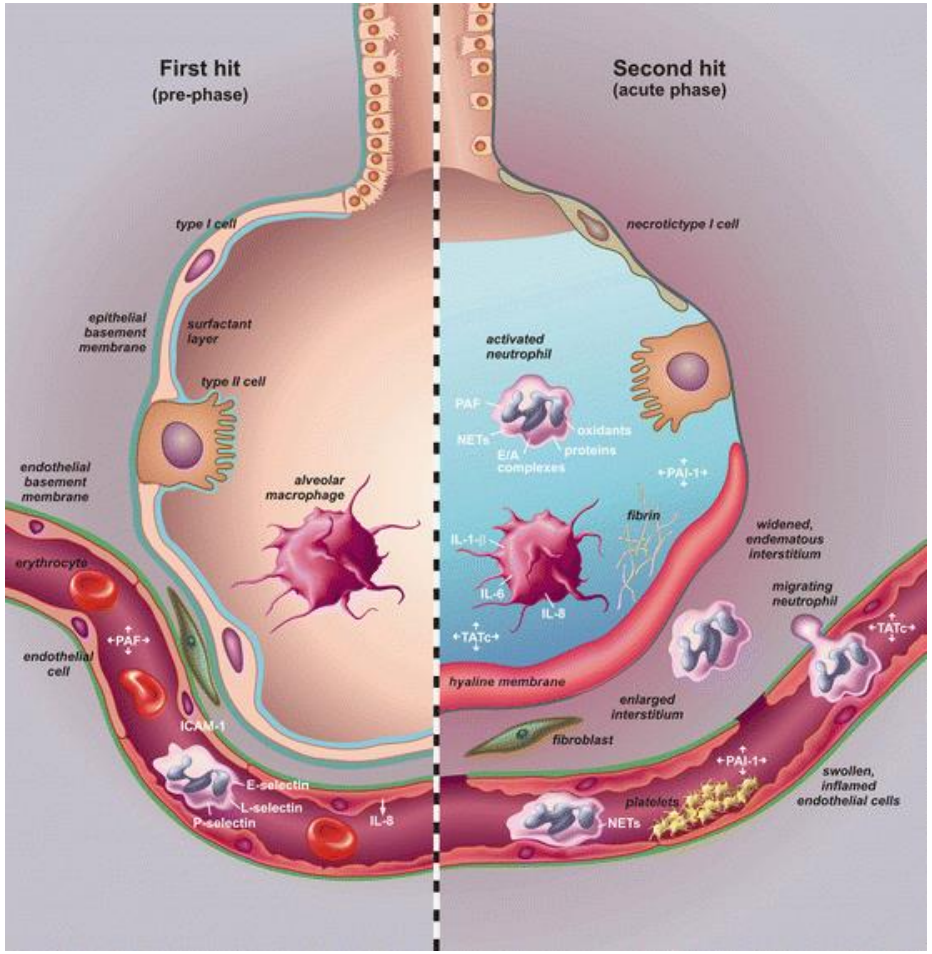
Transfusion-related Acute Lung Injury (TRALI)

Pathophysiology

- Capillaries are congested, endothelial cells are swollen and inflamed, and there is increased platelet deposition and aggregation. The interstitial becomes more enlarged. There is increased adherence and migration of neutrophils of activated adhesion molecules.



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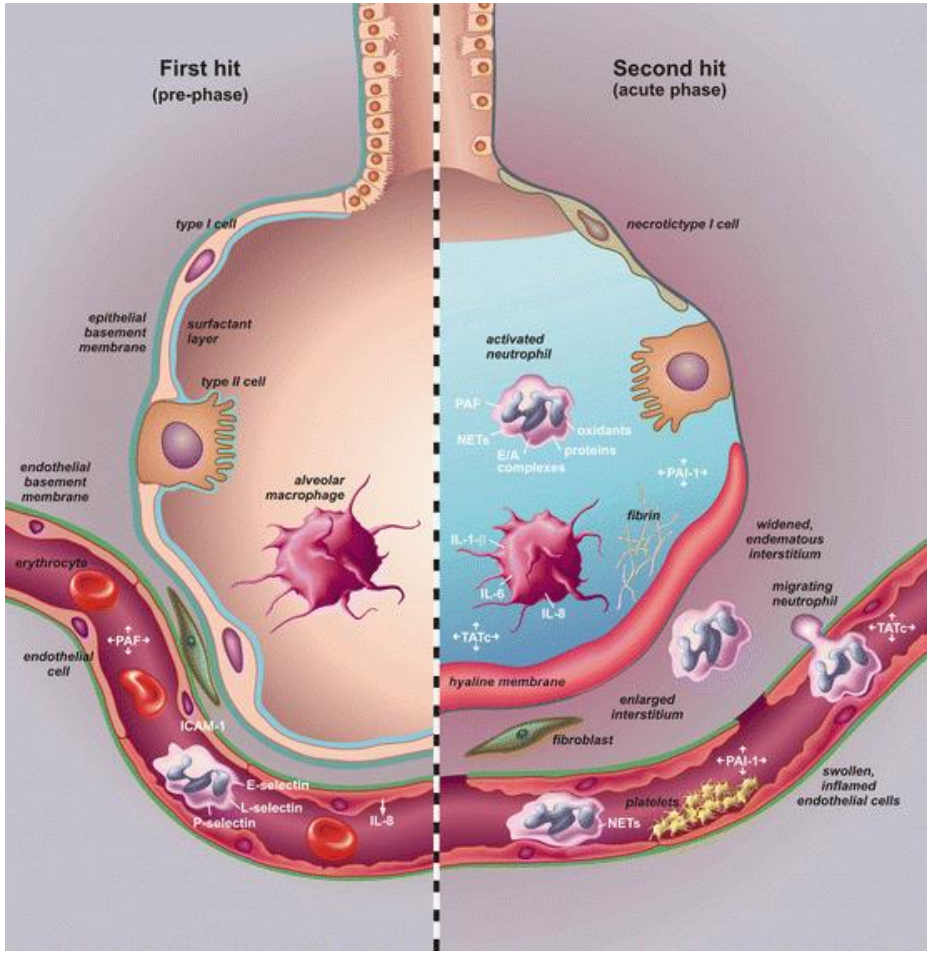
Transfusion-related Acute Lung Injury (TRALI)

Pathophysiology

- Also, alveolar macrophages liberate inflammatory cytokines (IL-1b, IL-6, IL-8) and activated neutrophils resultanting in capillary injury.
- All these culminated in lung injury with noncardiogenic pulmonary edema causing hypoxemia, hypotension, pulmonary infiltrates, and fever.



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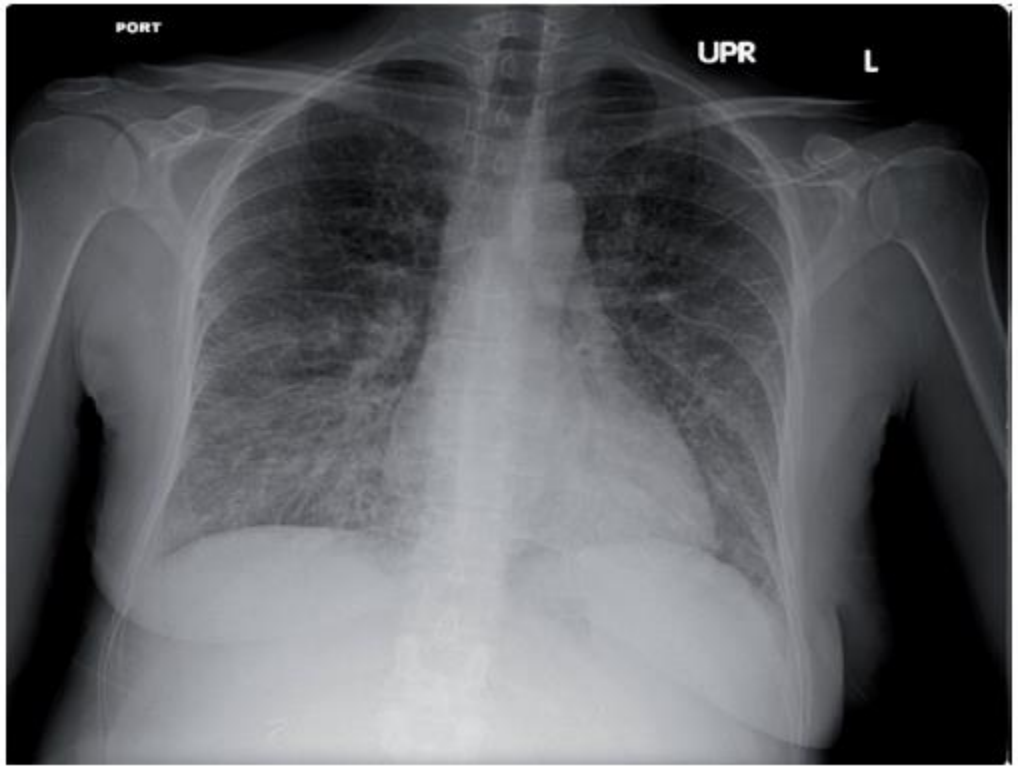
Transfusion-related Acute Lung Injury (TRALI)

Features

- Chest X-ray shows
  - Bilateral nodular shadowing in the lung fields with normal heart size.
  - Bilateral lung infiltrates with pulmonary edema
  - TRALI is often confused with acute heart failure due to circulatory overload



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Transfusion-related Acute Lung Injury (TRALI)

Management

- Clinical management is supportive with the goal of reversing progressive hypoxemia.
- There is no universal method to prevent TRALI.
- Once blood from a particular patient is implicated in a case of TRALI, the donor is excluded from the donor pool.
- Prevention of TRALI requires the elimination of all blood donors whose plasma contain anti-HLA or antineutrophil antibodies.
    - For plasma, this is achieved by excluding female donors from the plasma donor pool because multiparous females.

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Transfusion-Associated Circulatory Overload (TACO)

Definition

- Transfusion Associated Circulatory Overload (TACO) is defined as acute or worsening pulmonary oedema within 6 hours of transfusion.
- Typical features include acute respiratory distress, tachycardia, raised blood pressure and evidence of positive fluid balance.

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Transfusion-Associated Circulatory Overload (TACO)

World Health Organization

Presentation

- TACO may manifests as
  - Shortness of breath, cough, chest tightness,
  - Cyanosis, rales, orthopnea tachycardia, distended jugular veins, S3 gallop, and
  - Pulmonary edema, which are consistent with cardiac decompensation following volume overload

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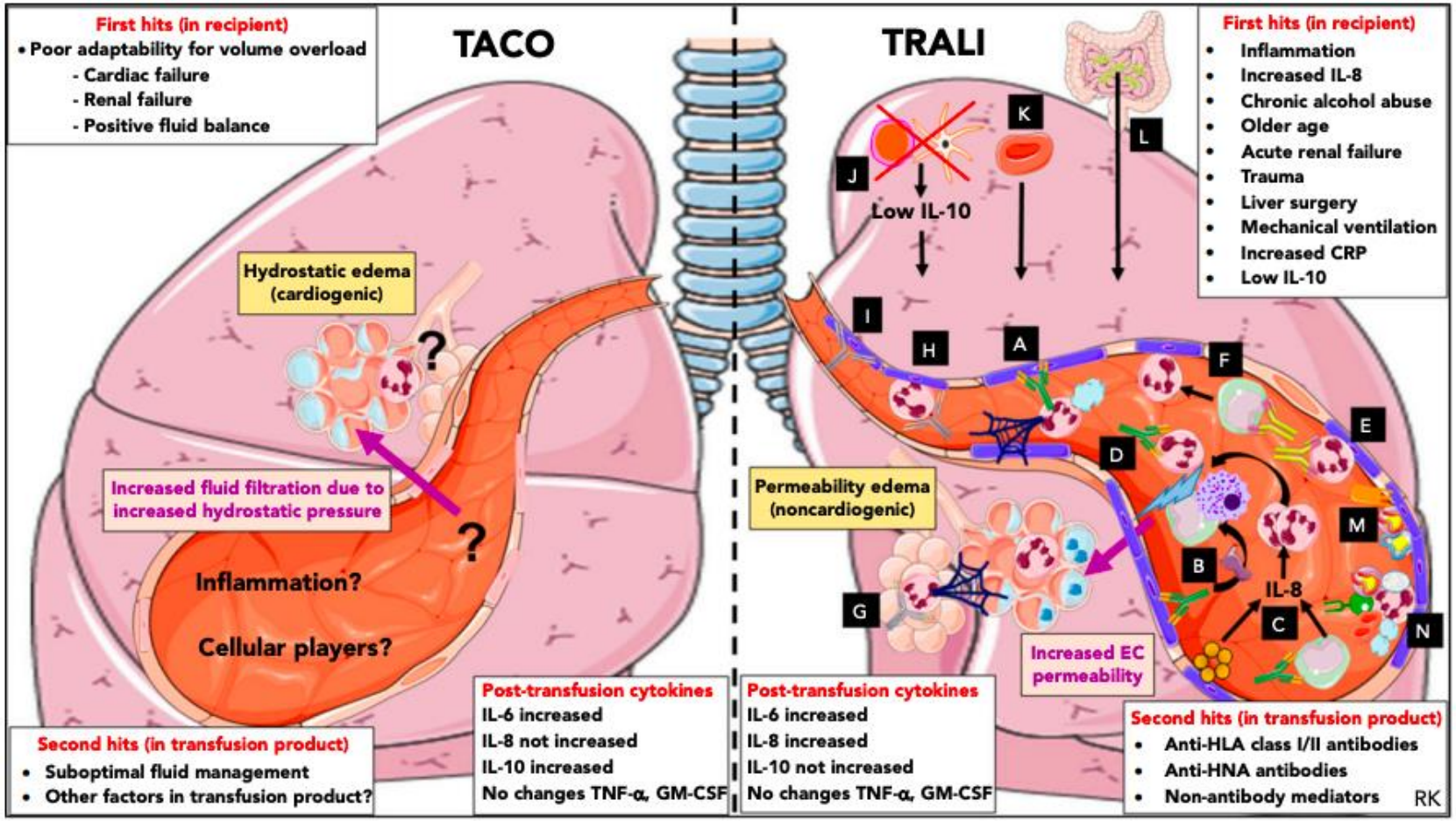
TRALI vs TACO



John W. Semple, Johan Rebetz, Rick Kapur; Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood* 2019; 133 (17): 1840–1853

TRALI vs TACO

Key diagnostic feature	Specific diagnostic readout	TACO	TRALI
Acute onset of respiratory distress symptoms	Onset <6 h upon blood transfusion	Yes	Yes
Hypoxemia	SpO_2 < 90% or PaO_2/FiO_2 < 300 mm Hg on room air	Yes	Yes
Pulmonary edema	Bilateral infiltrates on chest radiograph	Yes	Yes
Alternative risk factors for ALI	eg, pneumonia, sepsis, aspiration, multiple trauma, acute pancreatitis	No	No
			Yes: possible TRALI
Hydrostatic pulmonary pressure increased	Pulmonary artery occlusion pressure >18 mm Hg	Yes	No
Protein-poor edema fluid	Edema or plasma protein concentration <0.65 at the onset of acute respiratory failure	Yes	No
Increased ventricular filling/myocardial stretching[32-34]	B-type natriuretic peptide (BNP) >250 or pre-/posttransfusion BNP ratio >1.5 or N-terminal pro-BNP >1000 pg/mL	Yes	Yes*/No
Response to diuretics	Rapid and significant improvement	Yes	No
Cardiogenic nonlaboratory evidence for circulatory overload	Systolic ejection fraction <45 and no severe valvular heart disease on echocardiography	Yes	No
	Systolic blood pressure >160		
	Vascular pedicle width >65 mm and cardiothoracic ratio >0.55 on chest radiograph		
Cardiac ischemia	New ischemic changes on electrocardiography or new troponin T levels of >0.05	No	No

John W. Semple, Johan Rebetz, Rick Kapur; Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood* 2019; 133 (17): 1840–1853

Hypotensive Reactions

Definition

- Hypotensive reactions are indicated by
  - An isolated fall in systolic blood pressure of 30 mm Hg or more (to <80 mm Hg)
  - During, or within one hour of, transfusion
  - With no evidence of an allergic reaction or haemorrhage.
- Most are transient but they occasionally progress to shock and organ dysfunction.

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Hypotensive Reactions

Pathophysiology

- The cause of most of these reactions is unknown, although they may be more common in patients taking ACE inhibitors.
- Management involves stopping the transfusion and nursing the patient flat with leg elevation (or in the ‘recovery position’ if consciousness is impaired).
- Patients with recurrent hypotensive reactions may be given a trial of washed blood components

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Delayed Haemolytic Transfusion Reactions (DHTR)

World Health Organization

Definition

- Delayed Haemolytic Transfusion Reactions (DHTR) occur more than 24 hours after transfusion in a patient who has previously been ‘alloimmunised’ to a red cell antigen by blood transfusion or pregnancy.
- Antibodies to the Kidd (Jk) blood group system are the most common cause of DHTRs reported to SHOT, followed by antibodies to Rh antigens.

Delayed Haemolytic Transfusion Reactions (DHTR)

Pathophysiology

- Some Patients develop an alloantibody to an RBC antigen following previous transfusion, pregnancy, or HSCT.
- The antibody may have fallen to a level that is undetectable by the pre-transfusion antibody screen and the patient is then inadvertently re-exposed to red cells of the immunising group.

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Delayed Haemolytic Transfusion Reactions (DHTR)

Clinical Manifestation

- Clinical manifestation of DHTRs occurs
  - 5–15 days post transfusion
  - Comprises haemoglobinuria, jaundice, and pallor

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Delayed Haemolytic Transfusion Reactions (DHTR)

Lab Feature

- **Direct antiglobulin test** (DAT) is often positive for IgG, with or without compliment, depending on the antibody if carried out at this point.
- An **Eluate** may be performed to remove the IgG coating the circulating RBCs in order to identify it because a positive DAT may be unspecific.
- The **Antibody screen** may also demonstrate the presence of a new antibody, although this may lag behind a positive DAT by a few days.
- The antibodies most often implicated in DHTRs are directed against antigens in the Rh (34%), Kidd (30%), Duffy (14%), Kell (13%), and MNSs (4%)

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Delayed Haemolytic Transfusion Reactions (DHTR)

Management

- Usually supportive, sometimes requiring further transfusion.
- The offending antibodies must be recorded on the transfusion laboratory computer and medical records and patients are usually issued with an ‘Antibody Card/ report’ to carry and present to clinical staff whenever further transfusion is required.

Transfusion Associated Graft-versus-host Disease (TA-GVHD)

World Health Organization

Definition

- Rare and almost always fatal complication
- When viable lymphocytes in a blood donation engraft in the patient and mount an immune response against the recipient's cells of a different HLA type.

Transfusion Associated Graft-versus-host Disease (TA-GVHD)

World Health Organization

Risk

- **At-risk patients** usually have impaired cell-mediated immunity and are unable to reject the foreign cells.
  - Fetuses receiving intrauterine transfusion,
  - Inherited immunodeficiency disorders affecting T-cell function,
  - Medical procedures causing very severe immunosuppression such as allogeneic stem cell transplantation or on specific chemotherapy such as purine analogues
- TAGvHD has occasionally been reported in non-immunosuppressed patients receiving a blood transfusion from an HLA-matched donor or a close relative with HLA types in common.

Transfusion Associated Graft-versus-host Disease (TA-GVHD)

World Health Organization

Presentation

- Symptoms classically occur 7 to 14 days (maximum 30 days) after transfusion:
  - Fever, skin rash, diarrhoea, disturbed liver function and worsening bone marrow aplasia.
- Diagnosis is based on showing the typical features of acute GvHD in biopsies of affected organs and demonstration of donor-derived cells or DNA in the patient's blood or tissues.

Transfusion Associated Graft-versus-host Disease (TA-GVHD)

World Health Organization

Management

- Use of Irradiated blood components can prevent TA-GVHD
- Routine leucodepletion of blood components has clearly reduced the risk of TA-GvHD but it remains essential to ensure that all at-risk patients receive irradiated red cells or platelet components.

Post-Transfusion Purpura (PTP)

Definition

- Post Transfusion Purpura (PTP) is caused by re-stimulation of platelet-specific alloantibodies in the patient that also damage their own (antigen-negative) platelets by an ‘innocent bystander’ reaction.
- Affected individuals develop a very low platelet count and bleeding 5 to 12 days after transfusion of red cells.

Post-Transfusion Purpura (PTP)

Presentation

- The typical patient is a parous female who is
  - Negative for a common platelet antigen, (HPA-1a),
  - Initially sensitised by carrying a HPA-1a positive fetus in pregnancy.
  - This severe, and potentially fatal, complication has become rare since the introduction of leucodepleted blood components.

Post-Transfusion Purpura (PTP)

World Health Organization

Management

- Platelet transfusions are usually ineffective (but may be given in high doses in patients with life-threatening bleeding)
- Some patients show a prompt and sustained response to high-dose intravenous immunoglobulin (IVIg).

Iron Overload

Definition

- Excess iron absorption and transfusional iron intake cause iron accumulation in the liver, endocrine organs, heart, and other tissues with severe, life-threatening consequences.
- Blood transfusion burden is an important measure of total body iron balance.
- Ferritin is a relatively inexpensive and widely-available measure, useful in monitoring chelation therapy.

Wood JC. Diagnosis and Management of Transfusion iron overload: The role of Imaging. Am J Hematol 2007 Dec;82(12):1132-1135

Iron Overload

Definition

- Labile Plasma Iron (LPI) measurements show promise for predicting endocrine and cardiac iron toxicity, although existing LPI assays require more refinement, standardization, and clinical validation.
- Liver iron concentration reflects total body iron stores, but incompletely stratifies the risks of iron overload complications

Wood JC. Diagnosis and Management of Transfusion iron overload: The role of Imaging. Am J Hematol 2007 Dec;82(12):1132-1135

Key Points

- Appropriate categorization of adverse transfusion reactions is essential for appropriate management as well as reporting.
- Differentiation based on the clinical signs & symptoms of acute and delayed transfusion reaction is important in identifying the reaction
- Rapid recoganization and management of transfusion reaction may save patient’s life specially in acute reaction

World Health Organization

Thank you !

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