Immunologic Reaction to Transfusion

Dr. Mukesh M Desai
Prof. Pediatric Hematology Oncology (DNB)
Bai Jerbai Wadia Hospital
Chief, Division of Immunology
Consultant Hematologist & Immunologist
Sir H N Hospital
Balbhai Nanavati Hospital
Asian Heart Institute

Allogenic Blood Transfusion results in infusion in to the recipient of large no of soluble & cell bound antigens. The persistence of these antigens results in downregulation of the immune system. TRIM as it is known can be beneficial in renal transplantation or Crohn’s disease; but may aggravate risk of recurrence in cancer patients or may result in higher incidence of post operative infections. How much of this is fact or fiction is one of the most hotly debated topic in the transfusion medicine.

Patients of Immune Hemolytic Anemias require special consideration for grouping diagnosis and management. AIHA requiring transfusions pose a difficult challenge for Blood Bankers and clinicians. Besides a large no of adverse reaction to transfusions are immunologically mediated. In this brief review some of these aspects will be discussed.

Any adverse reaction that occurs during the administration of blood and blood component must be considered as transfusion reaction unless proved otherwise. Transfusion reactions occur in 7% to 10% of all recipient of blood or blood components. Fortunately, majority of them are minor reactions. 10% of these reactions are hemolytic and 90% of these are nonhemolytic reactions. Incidence of ABO mismatch blood being infused is 1 : 30,000 blood bag. 1 out of 10 ABO mismatch transfusion is fatal.

Transfusion reactions may be divided as follows:

**Acute ( <24 hrs ) :**

<table>
<thead>
<tr>
<th>Immunologic:</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic transfusion reaction</td>
<td>ABO incompatibility</td>
</tr>
<tr>
<td>Febrile non-hemolytic transfusion reaction</td>
<td>Cytokines, anti leucocyte antibodies</td>
</tr>
<tr>
<td>Allergic</td>
<td>Antibodies to plasma proteins</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Antibodies to IgA</td>
</tr>
<tr>
<td>TRALI</td>
<td>Antibodies to leucocytes or complement activation</td>
</tr>
</tbody>
</table>
Delayed adverse reaction to transfusion (> 24 hrs):

**Immunologic:**
- Alloimmunization to RBC, WBC, platelets
- Hemolytic
- TAGvHD
- Post Transfusion Purpura
- Immunomodulation

**Etiology**
- Exposure to antigen of donor origin-Plasma protein, HLA.
- Anamnestic antibody to RBC antigen.
- Engraftment of transfused functional lymphocytes.
- Antiplatelet antibodies.
- Not well understood.

**RECOGNITION OF ACUTE TRANSFUSION REACTION:**

**Signs and symptoms of Acute hemolytic transfusion reaction:**
1) Fever with or without chills
2) Rigors with or without fever
3) Pain at infusion site or in chest, abdomen or flanks.
4) Acute hypotension or hypertension.
5) Tachypnea and hypoxemia.
6) Nausea with or without vomiting.
7) Hemoglobinuria.
8) Urticaria, flushing, itching or edema.

**THE ROLE OF TRANSFUSIONIST IN CASE OF AN ACUTE TRANSFUSION REACTION:**

*First is to suspect and then is to take action.*

1) **STOP** Transfusion immediately.
2) **NOTIFY** responsible physician.
3) **MAINTAIN IV LINE** with normal saline drip.
4) **CHECK** for all identifying information for clerical error.
5) **Notify** Blood bank personnel and patient’s physician immediately.
6) Conditions requiring aggressive management need to be ruled out immediately. A physician must evaluate to rule out Acute hemolytic transfusion reaction, Anaphylaxis, TRALI, transfusion induced sepsis.
7) **Initiate** therapeutic actions.
8) Collect blood samples for the blood bank as directed by them usually 3-cc EDTA blood and 5 cc in plain tube.
9) Blood for coagulation profile in a 10cc-citrate tube and plain tube for biochemistry, electrolytes and appropriate blood cultures.

10) Return discontinued blood bag along with IV administration set, attached IV solutions, all related forms and labels.

11) In case the reaction is limited to urticaria or circulatory overload there is no need to evaluate post reaction blood or urine samples.

12) Observe the post reaction urine sample for AIHTR.

13) Monitor hemodynamic status, urine output, ECG.

THE ROLE OF BLOOD BANK LABORATORY.

a) Check for identification error: Recheck all the steps of transfusion process.

In case of misidentification search for other patients at risk.

b) Visual check for hemolysis: Post reaction plasma for hemoglobinemia. Elevated bilirubin by 5-7 hrs. Post reaction urine sample for hemoglobinuria

c) Serological check for incompatibility: DAT testing.

FEBRILE NON HEMOLYTIC TRANSFUSION REACTION: (FNHTR)

Definition:

- Rise in temperature of 1 degree Celsius with or without rigors.

Incidence:

- Common 0.5 to 1 %.
- Higher incidence in multiple transfused and multiparous females.

Etiology:

- Antibodies to leucocytes; Cytokine release.

Clinical picture:

- Fever with or without chills.
- Mild temperature rise early in transfusion or 1 to 2 hr later which is responsive to antipyretic.

Warning sign:

- Severe rigors, temperature more than 40 degree Celsius suggests bacterial sepsis.

Recurrence:

- 1 out of 7 with previous FNHTR.

Management:

- Diagnosis of exclusion.
- Stop transfusion till hemolytic transfusion reaction ruled out.
- Restart blood transfusion slowly.
- Supportive treatment with Chlorpheniramine 50 mg & paracetamol.

Prevention:

- Use leucodepletion filters if patient has more than 2 FNHTR.
- Use saline washed RBCs.
- Premedication with paracetamol.
ALLERGIC URTICARIAL REACTION:

Incidence: • 1 to 3%

Etiology: • Antibodies to donor plasma proteins.

Clinical picture: • Itching, urticaria, rash, flushing and rarely laryngeal edema & Bronchospasm. It occurs towards the end of transfusion or after transfusion.

Management: • No need to stop transfusion
 • IV Chlorpheniramine
 • IV Hydrocortisone
 • Subcutaneous adrenaline 1:1000 if there is laryngeal edema

Prevention: • Prophylactic Chlorpheniramine
 • Saline washed RBC.

ACUTE IMMUNE HEMOLYTIC TRANSFUSION REACTION (AIHTR):

Incidence: • 1: 30 000 blood bag transfused in Britain
 • 1: 33 000 to 1 : 12000 in USA.

Fatality rate: • Commonest cause of transfusion related mortality.
 • 1: 10 reaction in Britain.
 • 6% in USA.

Etiology: • Almost always due to ABO mismatch blood transfusion.
 • Rarely due to anti Lewis, anti P and anti H.
 • Occur in emergency, ICU setting or in operation theatre.
 • Invariably due to human error.
 • Clerical error in labeling or mix-up of samples.
 • Technical error in grouping and compatibility testing.

Pathophysiology: • Catastrophic event following hemolytic reaction when transfused RBCs interact with preformed antibodies in recipient.
 • Severity is related to amount of blood transfused. Reaction may occur with as little as 10 to 15 ml of blood.
 • Most reactions occur in the first ½ hr of starting the transfusion.
 • Neuroendocrine response:
   • Ag +Ab + XIIa –activation of kinin bradykinin pathway. Increased capillary leak, vasodilatation, shock and hypotension.
   • Complement activation: C3a-C5a – shock, hypotension, bronchospasm
   • C5-9- hemolysis
   • Coagulation activation: DIC.
   • Cytokines release: IL 6, 8, TNF alpha- fever, hypotension,
   • Activation of coagulation pathway, DIC, Renal failure.

Clinical features:
**Symptoms:**
- Chills, flushing, sweating, chest pain, pain at infusion site, back pain, abdominal discomfort, nausea, vomiting and restlessness.

**Signs:**
- Fever with rigors, hypotension, tachycardia, hemoglobinuria, dyspnea, anuria / oliguria, tachypnea, cyanosis, pallor, shock and DIC.

**Unconscious patients:**
- Uncontrolled bleeding (DIC)
- Hypotension
- Hemoglobinuria

"Any febrile reaction is treated as AIHTR unless proven otherwise."

**TREATMENT and work up of AIHTR:**
- STOP BLOOD COMPONENT TRANSFUSION IMMEDIATELY
- Maintain IV access with crystalloid
- Maintain Blood pressure, pulse
- Maintain adequate ventilation
- Give a diuretic and/or institute fluid diuresis
- Obtain blood urine for transfusion reaction workup
- IF INTRAVASCULAR HEMOLYSIS IS CONFIRMED,
  - Monitor renal status (BUN, Creatinine)
  - Monitor coagulation status (PT, PTT, fibrinogen, FDP)
  - Monitor for signs of hemolysis (bilirubin, LDH, haptoglobin)

  If sepsis is suspected send appropriate cultures.

**PREVENTION:**
- Minimize human error
- Delineation of every step from phlebotomist to medical technologist to Transfusionist.
- Education of transfusionist as he has the last opportunity to prevent misidentification and the first one to identify transfusion reaction.

**ANAPHYLACTIC REACTION:**

**Incidence:**
- 1 : 1,70,000
- 1 : 18,000

**Etiology:**
- Antibody to donor plasma protein.
- Most commonly Anti IgA
Clinical features:

- Occurs after infusion of few ml of blood. Cough, bronchospasm, respiratory distress, Abdominal cramps, diarrhea, shock, loss of consciousness and absence of fever

Treatment:

- Stop transfusion
- Treat shock
- Epinephrine 0.3 to 0.5 mg C or IM 1 : 1000 solution. In severe cases 1 : 10 000 IV
- Steroid: IV hydrocortisone 100 mg
- Antihistaminic IV, B2 agonist.

Prevention:

- TRANSFUSE BLOOD COMPONENT THAT LACK IgA
- Maintain donor file.
- Deglycerolized RBC
- Extensively washed RBC
- Encourage Autologous blood transfusion.
- Plasma component prepared from IgA deficient individuals.

TRALI (Transfusion related acute lung injury)

Incidence:

- Rare

Etiology:

- Anti HLA or Leucoagglutinin

Pathophysiology:

- Migration of activated neutrophils to lung.
- Release of inflammatory mediators TNF alpha, IL1.
- Microvascular occlusion.
- Capillary leakage and pulmonary edema.

Clinical presentation:

- Idiosyncratic presentation with in 4 hrs of transfusion
- Marked respiratory distress.
- Hypoxia, hypotension, fever.
- Bilateral pulmonary infiltrate.

Treatment:

- High dose steroids
- Supportive care
- Ventilator support.

Prevention:

- Washed RBC.
- Microaggregate filters.
Leucodepletion for blood and blood component.

**TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE:**

**INCIDENCE:**
- Very rare
- 1:660 in Japan

**Etiology:**
- Transfusion of viable lymphocytes
- which engraft in the recipient,
- proliferate and initiate GvHD
- Immunocompromised host
- HLA compatible donor
- Blood relative
- HLA matched component
- Population with limited HLA diversity.

**Target organs:**
- skin, Liver, Gastrointestinal tract, Bone marrow

**Clinical features:**
- Begins by 10th to 12th day
- Erythroderma
- Jaundice and liver enzyme abnormalities
- Diarrhea 3 to 4 liters of watery diarrhea
- Pancytopenia

**Diagnosis:**
- HLA typing
- Skin biopsy

**Patient at risk:**
- Neonate, premature babies, Premature with Hemolytic disease of newborn (HDN), intrauterine transfusion, Full term and HDN requiring Exchange transfusion, Full term with neonatal alloimmune thrombocytopenia requiring mothers' platelets.
- Congenital immune deficiency: SCID, Wiskott Aldrich syndrome, Purine nucleotide phosphorylase deficiency and Nezloff syndrome.
- Fresh maternal and paternal plasma
  Leukemia estimated risk 0.1 to 1%
- Lymphoma estimated risk 2%
- Post BMT
- HLA matched allogenic BMT
- Transfusion from blood relative
- HLA matched blood component
• Donor of the same ethnic background with limited HLA diversity
• Solid tumors on intensive chemotherapy.

**Components implicated in TAGvHD:**
- Whole blood
- Packed cells
- Granulocyte pack
- Platelets
- Fresh plasma

**Components not implicated in TAGvHD:**
- FFP
- Cryoprecipitate

**Comparison of TAGvHD and GvHD in BMT**

<table>
<thead>
<tr>
<th></th>
<th>TAGvHD</th>
<th>BMT GvHD</th>
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<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>0.1 to 1.0%</td>
<td>0.2 30 to 70%</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>2-47 days</td>
<td>35 to 70 days</td>
</tr>
<tr>
<td><strong>Pancytopenia</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>BM</strong></td>
<td>Hypocellular</td>
<td>not affected</td>
</tr>
<tr>
<td><strong>Duration of illness</strong></td>
<td>&lt;54 days</td>
<td>5 months</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>87–100%</td>
<td>5 – 10%</td>
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</table>
**PREVENTION:**

- Irradiation of blood and blood component for patients at risk. Dose: 2500
- Irradiation of :
  - Cellular component intrauterine transfusion
- Patients identified at risk for TAGvHD
- Transfusion of cellular component between blood relatives
- Transfusion of HLA selected products

**MORTALITY:**

- 87 TO 100%

**DELAYED HEMOLYTIC TRANSFUSION REACTION:**

**Two types :**

- Anamnestic response to transfused RBCs
  Primary alloimmunisation.

**Incidence**

- 1 : 11000 to 1 : 5000
- 0.05% to 0.07% of transfusion recipient.

**Clinical presentation :**

- More common in multiply transfused & Multiparous women
- Occurs 3 – 7 days post transfusion.
- Extravascular hemolysis.
- Absence of anticipated Hb or HCT rise following blood
- Transfusion.
- Jaundice
- Fever
- Rarely hemoglobinuria

**Antibodies implicated :**

- Common antibodies
  - Anti jka
  - Anti E
  - Anti D
  - Anti C
  - Anti K
  - Anti Fya
- Rarely Anti HLA antibodies.

- uncommon antibodies
  - Anti A1
  - Anti P1

**Investigations :**

- Freshly draw blood to test for alloantibodies,
  Compare with previous sample.
**Treatment**:
- Rarely necessary
- Observe urine output
- Blood transfusion that lack the corresponding antigen.

**Prevention**:
- Blood that lack the responsible antigen.
- Issue medical alert card to these patients
- Maintain record of the offending antibodies.

**POST TRANSFUSION PURPURA**:

**Incidence**:
- Uncommon

**Presentation**:
- Acute severe thrombocytopenia 5 – 10 days after transfusion in a previously pregnant female or multiply transfused individual.
- Typically peri menopausal or menopausal women
- Rare in males.

**Pathophysiology**:
- Patients platelet lack HPA -1a (PLA1)
- 2 % of population
- Antibodies destroy both HPA-A1 positive and HPA-A1 negative platelets.

**Course**:
- Self limited, recovery in 21 days

**Treatment**:
- Steroids controversial
- Plasma exchange
- IV IgG
- HPA-A1 antigen negative platelet of benefit but difficult to arrange.

**Prognosis**:
- Good.
- Recurrence rare.

**Prevention**:
- Washed PC
- Blood from HPA-A1 negative patients.

**PLATELET REFRACTORINESS**:

**Incidence**:
- 20 to 70 % requiring multiple platelet transfusion

**Criteria**:
- Lack of accepted CCI of two platelet transfusion
  Poor response to three platelets in 2 weeks.

**Causes**:
- Platelet alloimmunization
Autoimmune Hemolytic anaemia (AIHA):
Besides problems of transfusion management in AIHA there is newer change in the epidemiology of AIHA which one should be aware of.

AIHA with Purine Nucleoside Analogue therapy:
23% of patients on Fludarabine developed AIHA and had a recurrence on re challenge.
AIHA also occurred with cladribine and pentostatin. 29% died due to complication of AIHA.

Association with Blood Tx:
Though alloantibodies formation is associated with allogenic Blood transfusion, AIHA can also occur following transfusion 41/2400 patient analysed post transfusion developed Autoantibodies along with alloantibodies. In 1/3rd there was a temporal association with the development of AIHA, Alloantibodies and transfusion. Thus AIHA may be a more frequent complication of AIHA. This condition may be more common than recognised and need be treated with iron supplements with Epo analogues. This is a major problem in multiply transfused patients especially Thalassaemics. iron supplements with Epo analogues. This is a major problem in multiply transfused especially Thalassaemics.

AIHA with allogenic HSCT:
Minor Blood group incompatibility: Donor blood group O and recipient blood group A or B:
This complication occurs when there is minor blood group incompatibility. Occurs most often when the Donor is blood group O and the recipient is group A. The hemolysis sets in early with in 2 wks of HSCT is severe and result in severe anaemia, intravascular hemolysis and occasionally renal failure. May occur in up to 10 to 15% of patients and is attributed to “The Passenger Lymphocyte Syndrome”. It is not due to passively transfused blood as it takes time for the hemolysis to set in. The rapidly dividing passenger lymphocyte produces IgG antibodies against Anti A or Anti B which is more common in group O patients resulting in severe
hemolysis. The hemolysis may also be due to antibodies against Anti D, anti E, anti s, anti jkb and jka. It occurs while before engraftment has occurred and while patient is pancytopenic. It very often subsides in 5 to 10 days as the residual recipient cells are lysed and replaced by the donor O group cells or transfused O group cells. Several risk factors are identified are Use of cyclosporine without MTX for GvHD prophylaxis, Reduced intensity conditioning, female Donor, non genotypically HLA matched donor and PBSC transplant. This condition is not noted with umbilical cord blood transplantation.

Clinical presentation is with a rapid onset of hemolysis which is often severe, DCT may be positive and anti A and anti B antibodies are identified with resultant intravascular hemolysis and sever renal failure.

Treatment strategies include
- Reduce plasma product in the HSC collection so as to minimize infusion of Anti A and Anti B. These are not responsible for hemolysis but it can result in case of transfusion of large volume,
- Transfusion support with either group O blood or compatible blood.
- In case the recipient is AB and Donor A or B group. Donor group cells can be used.
- Steroids is often used
- Plasma transfusion and platelet Tx support should be of recipient group so as to minimize more anti A and Anti B being infused to the recipient.
- Renal function should be maintained and monitored.
- In severe cases Exchange transfusion with group O blood to replace recipient group with O group advised.

**Major Blood group in compatibility: Donor Group A or B and recipient group O:**

Hemolysis can be prevented by removing RBC from the donor infusion
Persistence of recipients ABO antibodies result in persistent hemolysis for several months.

Many patients need transfusion support for several months with group O Blood.

Some patient also show more pronounced hemolysis by lysing transfused group O cells called “Bystander effect”. This effect where antibodies destroy red cells negative for antigens against which the antibody is directed is poorly understood.

**AIHA can also occur following HSCT:**

Donor immune system producing antibodies against Donor Red Blood Cells:
- This effect has been seen in 6 % of pediatric transplantation but can affect any age group. The mortality is extremely high as there is need for additional immunosuppression in a patient already receiving GvHD prophylaxis.
- More common among patients who were transplanted for metabolic disorder
- More common among T cell depleted HSCT
- Both warm and cold antibodies are being described.
- Cold antibodies tend to occur within 2 to 8 mths
- Warm antibodies tend to occur later between 6 to 18 mths
- Succesful treatment with Rituximab has been described.

**Association of immune hemolysis with orthotopic solid organ transplantation:**
- Association of immune hemolysis with solid organ transplantation is well described.
• Commonly seen when Donor is Blood group O
• AB recipient transplanted with non AB donors can also develop immune hemolysis.
• The mass of lymphocyte transplanted with solid organ decides the risk and degree of hemolysis.
• It is highest with Hear lung with 70% risk of hemolysis followed by liver transplantation risk of hemolysis of 29% and lowest in renal transplantation where the risk of hemolysis is 9%
• Hemolysis of rapid onset
• DAT is +ve
• Detectable serum antibody.
• Antibody is very often directed against Anti D onset is between 3 to 24 days
• Antibodies could be IgG, C3 or both combined.
• The transfusion requirement is 6.5 units
• The hemolysis is transient and very often subsides as the passenger lymphocytes donot engraft and donot proliferate indefinitely.

Management include
• Transfusion with group O red blood cells
• Avoid ABO incompatibility in plasma product
• Maintenance of adequate renal function
• Transfused RBC should be ABO identical or compatible with recipient serum.
• If the donor and recipient have different blood type, products should be used that are ABO-compatible with both the recipient and donor red cells, as well as the donor organ tissue type, to avoid transfusing antibody that may contribute to hemolysis.

AIHA and thrombosis:

ALHA patient are also prone to thrombosis. The hemolysis results in exposure and disruption of Red cell membrane allowing formation of prothrominase complex and result in thrombosis. A large no of AIHA also have associated Lupus anticoagulant and there is high risk of thrombosis. There must be other factors besides lupus anticoagulant which may be responsible as there is a higher incidence of thrombosis in patients who donot have associated lupus anticoagulant. Anticoagulation in AIHA in those patients who have higher incidence of thrombosis due to presence of lupus anticoagulant may be recommended.

Treatment of AIHA:

• Corticosteroids
• Splenectomy
• Immunosuppressive therapy

Newer therapy to be used in case of splenectomy failure includes:
• IvGG
• Danazol
• Rituximab
  o Response seen in refractory cases either when used alone or in combination with Cyclophosphamide and dexamethasone
  o Current flavor of season
• alemtuzumab

TRALI: Transfusion related Acute Lung injury:
Definition of TRALI: a new ALI (Acute Lung injury) with in 6 hrs of transfusion with a clear temporal relation to transfusion in a person with or without risk factor for Alien other than transfusion.
Limitation of above definition is time limit of 6 hrs, will miss mild TRALI, lack of laboratory criteria and severity of hypoxemia.
Subsequent definitions by Canadian consensus conference has added possible TRALI group and introduced subjectivity.

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</tr>
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<td>Worsening of preexisting pulmonary insufficiency temporally related to transfusion</td>
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<tr>
<td>Pulmonary insufficiency satisfies the criteria for the diagnosis of ALI.</td>
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*ALI occurred during transfusion or within 6 hours of the completion of transfusion.
†Recognition by the clinical care team that ALI is most likely caused by transfusion.

TRALI is very similar to ARDS occurring in the setting of transfusion. Patient present with respiratory distress, tachypnoea, hypoxemia, bilateral fluffy shadows on Xray with in 6 hrs and Signs and symptoms include tachypnoea with frothy sputum hypotension rarely hypertension and tachycardia cyanosis. Generally most patients require oxygen and ventilator support. There in no elevation of CVP and no gallop which helps differentiate TRALI from TACO (Transfusion associated Circulatory over load)
Typically recovery is seen with in 96 hrs with resolution of pulmonary infiltrate. Mortality rate today is between 5 to 10%. No laboratory tests are diagnostic and very rarely it is useful to
demonstrate presence of HLA I & II antibodies and these tests are not readily available. So at best the diagnosis is clinical.
The incidence of TRALI range from 1:5000 to 1:432; there is a huge variation and this reflects in lack of consensus in the definition of TRALI. TRALI has been reported after use of most blood products and the most commonly implicated product has been FFP. All products implicated with development of TRALI have at least 50 ml of plasma. TRALI has also been reported after IVGG therapy.
Pathophysiology of TRALI:
It is multifactorial and there is a strong immune basis for TRALI. Non immune mechanisms can also result in TRALI. The basic pathophysiology is activation of neutrophils with capillary leakage resulting in pulmonary infiltrates and this activation may be triggered by immune mechanisms like antibodies or due to a cytokine or biologic response modifier.

**Immune TRALI:**

65 to 90% of TRALI have anti Neutrophil antibodies in the donor plasma. Antibodies may be against HLA class I, II or neutrophils. The neutrophil antigen most commonly involved is 5b(HNA3a). In a small no of patients the antibodies are in the recipient directed against the donor Neutrophils. Donor characteristic involved with TRALi. Most of them are multiparous women with high incidence of sensitization to HLA class I & II antigens.
Transfusion of preformed antibodies bind on neutrophil antigen resulting in agglutination and sequestration in the lung and activation. Complements are activated and neutrophil released cytokines result in endothelial damage, capillary leakage and acute lung injury. HLA class II antigens are also expressed on monocytes and it may also contribute to TRALI.

**Non Immune TRALI:**
There are 15 % of cases who do not have antibodies. Not every patient with antibodies develops TRALI.
Non immune mechanism is a 2 hit theory. In 1st hit there is endothelial injury, activation with release of cytokines expression of adhesion molecules. Cytokine primes the neutrophils and sequesters them in the pulmonary capillaries. Events that lead to this activation are infection, sepsis, shock and massive transfusion. A 2nd hit results in activation of these neutrophils with release of cytokines, oxidases, proteases and enzymes resulting in capillary leakage and TRALI. The second hit may be due to biological response modifiers like antibodies, lipid priming molecules, cytokines, CD 40L or exotoxin.

**Prevention of TRALI:**
Deferral of Donors implicated in TRALI case. Typical donor who is implicated has a history of transfusion or is a multiparous woman. They can be screened for Anti HLA antibodies and screened for anti granulocyte antibodies. They are deferred from donation. One useful strategy is to use plasma donated by male donors only and utilize plasma from female donors exclusively for fractionation. Decreasing plasma contamination of components by using strategies like saline washing, additive suspension solution for platelets will reduce the risk of TRALI.
Table 1.
Definition of TRALI

TRALI without clinical risk factors for ALI
New ALI temporally related to transfusion*
Worsening of preexisting pulmonary insufficiency temporally related to transfusion

TRALI with clinical risk factors for ALI
New ALI temporally related to transfusion*
New ALI thought to be mechanistically related to transfusion†
Worsening of preexisting pulmonary insufficiency temporally related to transfusion
Pulmonary insufficiency satisfies the criteria for the diagnosis of ALI.

*ALI occurred during transfusion or within 6 hours of the completion of transfusion.
†Recognition by the clinical care team that ALI is most likely caused by transfusion.
Clinical Effects Of Contaminating Leucocytes

HLA Alloimmunisation
- Reactions
- Platelet Refractoriness
- Graft Rejection

Viral Transmission
- Cytomegalovirus (CMV)
- EBV, HTLV I & II, Varicella zoster

Immune Suppression
- Post Operative Infection
- Cancer Recurrence
- Latent Viral Reactivation

Consequences of HLA Antibody Production
- NHFTRs
- Granulocyte
- Rejection
- Organ / Graft
- Refractoriness
- Platelets
- Plasma

2,000 antibodies per second during 5–7 day lifespan
Clinical Effects Of Leucocytes

Transfusions

Contaminating Leucocytes

Reactions → Alloimmunisation → Cytomegalovirus → Immunosuppression

Platelet Refractoriness

No Platelet Increment

Infections → GVHD

Further Platelet Transfusions → Further Treatment

Cancer Recurrence

Increased Hospital Stay

Normal PMN response to infection

Intravascular:
- Random contact
- Rolling (E selectin, P selectin)
- sticking (selectins, integrins)
- Diapedesis (LFA-1, ICAM-1)
- chemotaxis (chemokines)

Extravascular:
- Bacteria
- Diapedesis
- Killing
- Chemotaxis

L selectin
Sialyl Lewis x
E selectin
P selectin
LFA-1
ICAM-1
Bacteria
Chemokines
PMN mediated Tissue Injury in TRALI

Random contact → Rolling → sticking → Diapedesis → chemotaxis

Intravascular

LPS/Lipids Cytokines

Transfusion or infection

Endothelial cell damage Capillary Leakage

Extravascular

PMN mediated Tissue Injury in TRALI

Random contact → Rolling → sticking → Diapedesis → chemotaxis

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Extravascular