

Fundamentals of Transfusion Reactions

Nicole Saviano, MD
Medical Director

1/10/2024



LifeServe
BLOOD CENTER

Your **Blood**. Your Hospital. Your Neighbors.

**Physician available 24/7
for:
Practitioners with transfusion
related and
Blood Bank related questions and
concerns**

515-309-4840



LifeServe
BLOOD CENTER

Your **Blood**. Your Hospital. Your Neighbors.

Outline

1. Acute Hemolytic Transfusion Reaction
2. Delayed Hemolytic Transfusion Reaction
3. Febrile Non-Hemolytic Transfusion Reaction (FNHTR)
4. Transfusion-Related Acute Lung Injury (TRALI)
5. Transfusion-Associated Circulatory Overload (TACO)
6. Allergic Reactions



LifeServe
BLOOD CENTER

Your **Blood**. Your Hospital. Your Neighbors.

Outline

7. Hypotensive Transfusion Reaction
8. Transfusion-Associated Dyspnea (TAD)
9. Delayed Serologic Transfusion Reaction
10. Transfusion Transmitted Infection
11. Post Transfusion Purpura
12. Transfusion-Associated Graft vs. Host Disease (TAGVHD)



LifeServe
BLOOD CENTER

Your **Blood**. Your Hospital. Your Neighbors.

Acute Hemolytic Transfusion Reaction

- Rapid destruction of RBCs during or within 24 hours of cessation of transfusion.
- There are notable clinical and laboratory signs and symptoms of hemolysis.



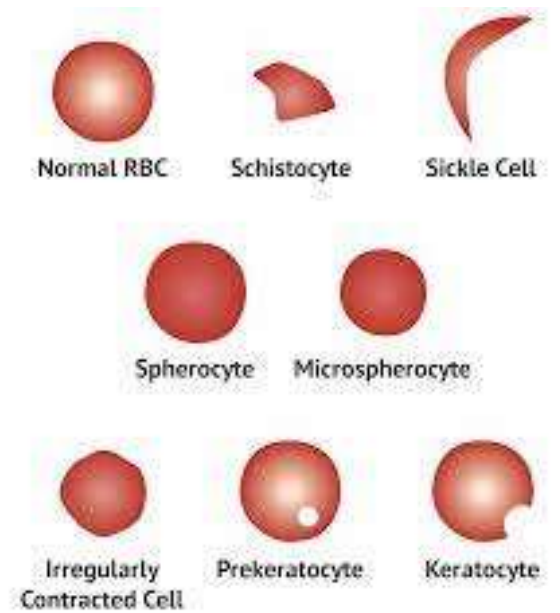
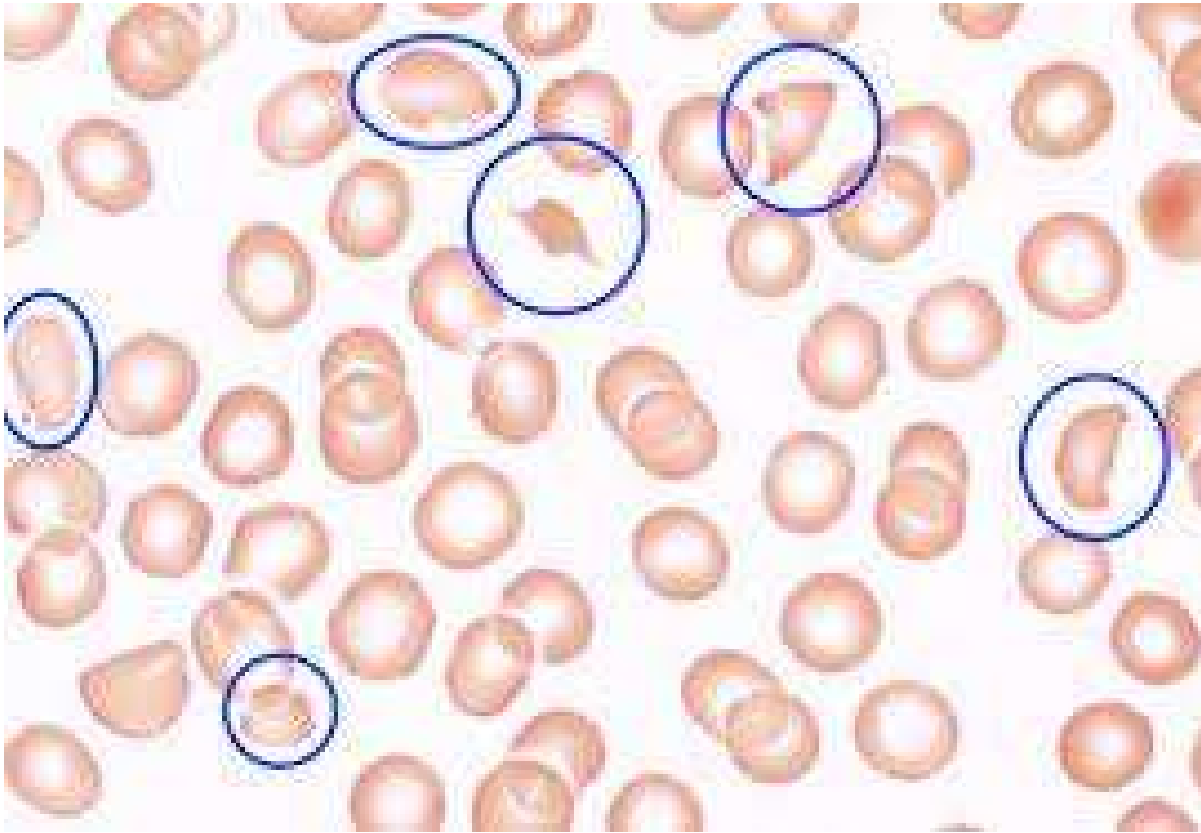
Causes:

- Transfusion of ABO-incompatible blood
 - Transfusion of ABO-incompatible plasma
 - Non-ABO antibodies
- 

Diagnosis

- Patient may show any of the following:
 - Fever, chills, rigors, flank pain, blood in urine, hypotension, oozing at an IV site or anuria/renal failure.
- With at least 2 of:
 - Decreased fibrinogen or haptoglobin
 - Elevated unconjugated bilirubin or LDH
 - Hemoglobinemia or hemoglobinuria
 - Plasma discoloration
 - Schistocytes and Spherocytes on peripheral blood smear examination



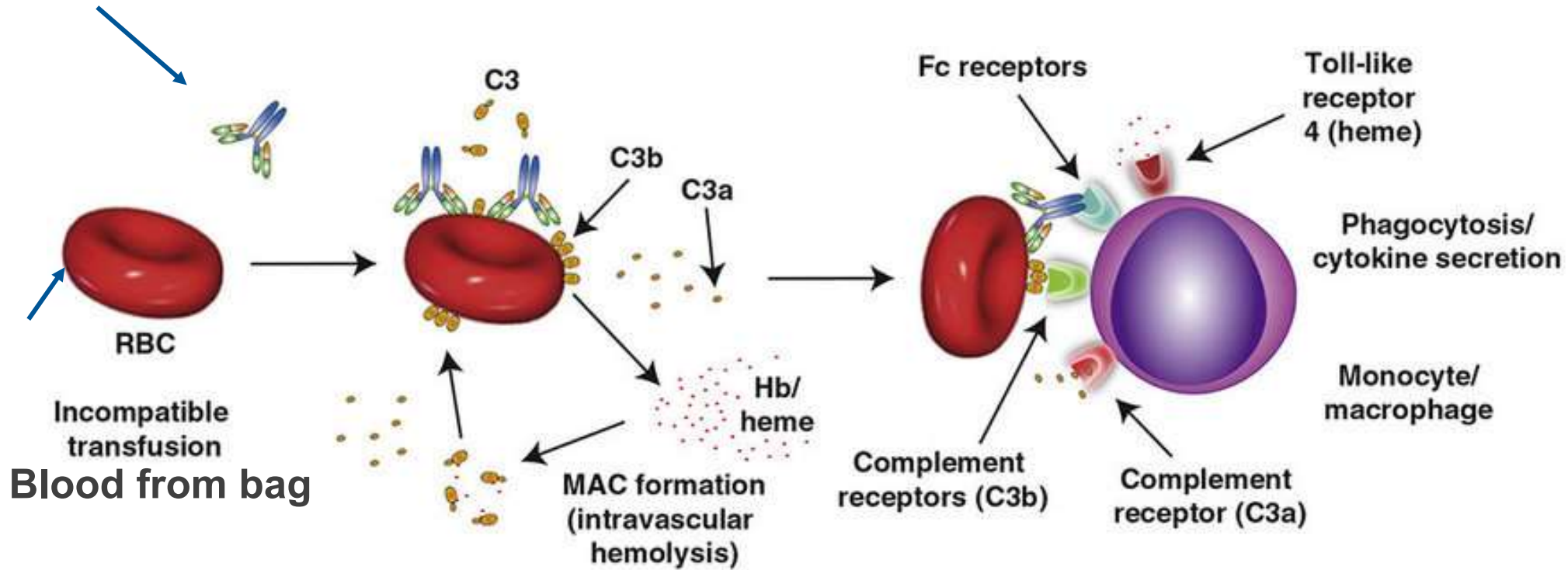


SCHISTOCYTES



Why does hemolysis occur:

Recipients antibody





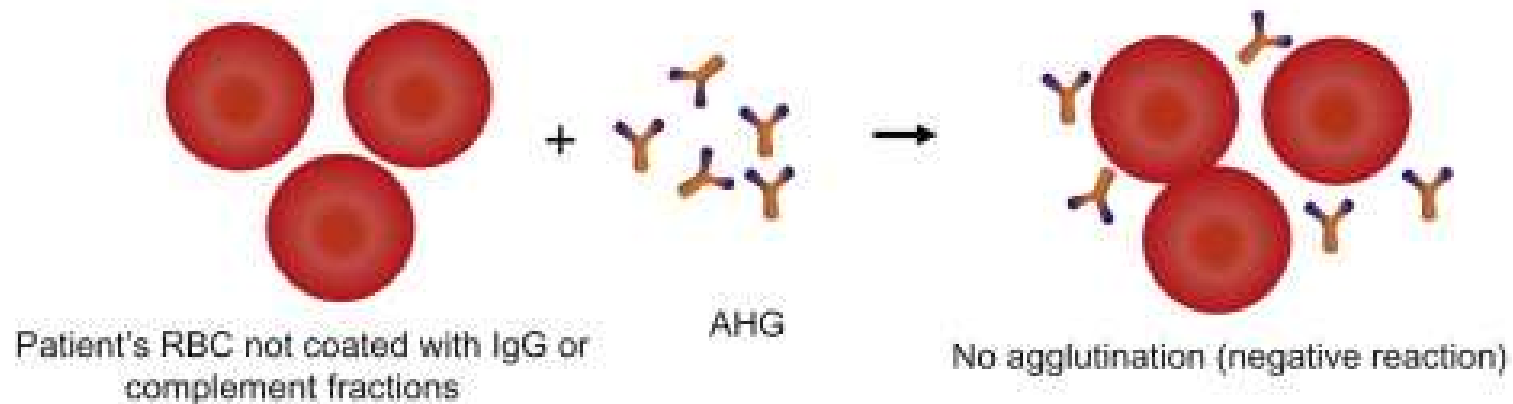
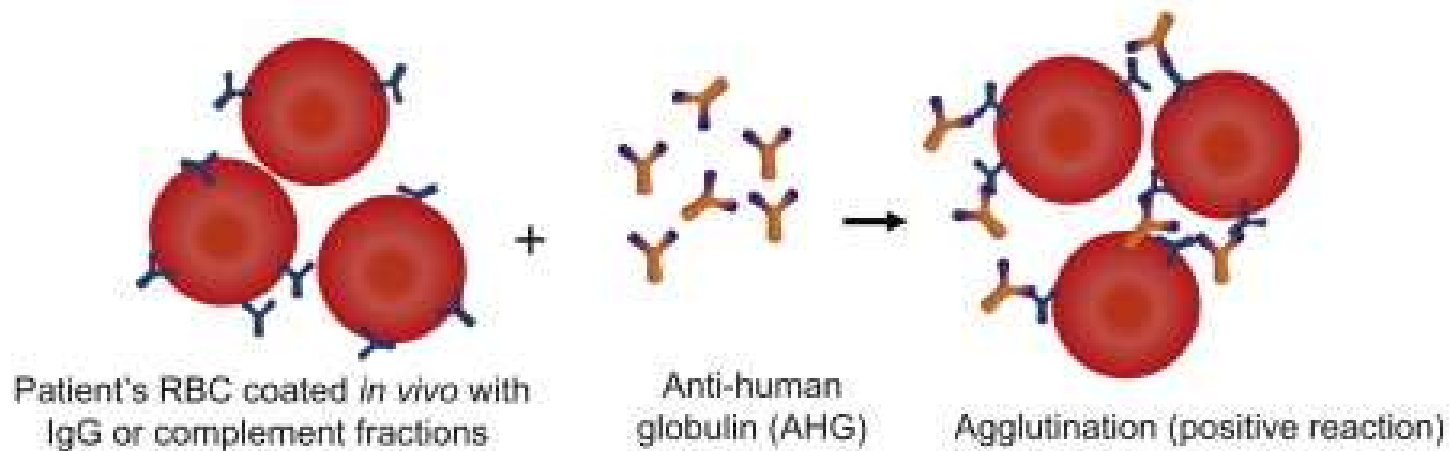
How do we prove this?

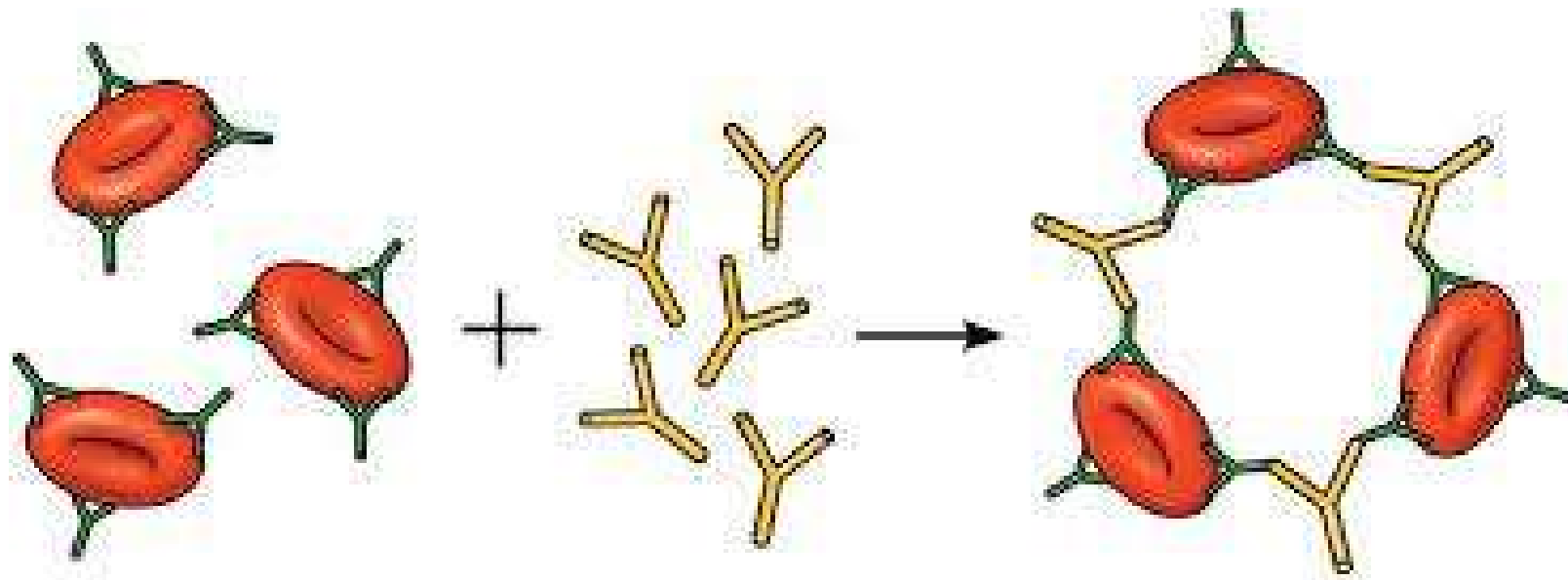
- A positive direct antiglobulin test using AHG (anti-IgG or anti-C3).
- Positive elution test revealing an alloantibody present on transfused red blood cells.

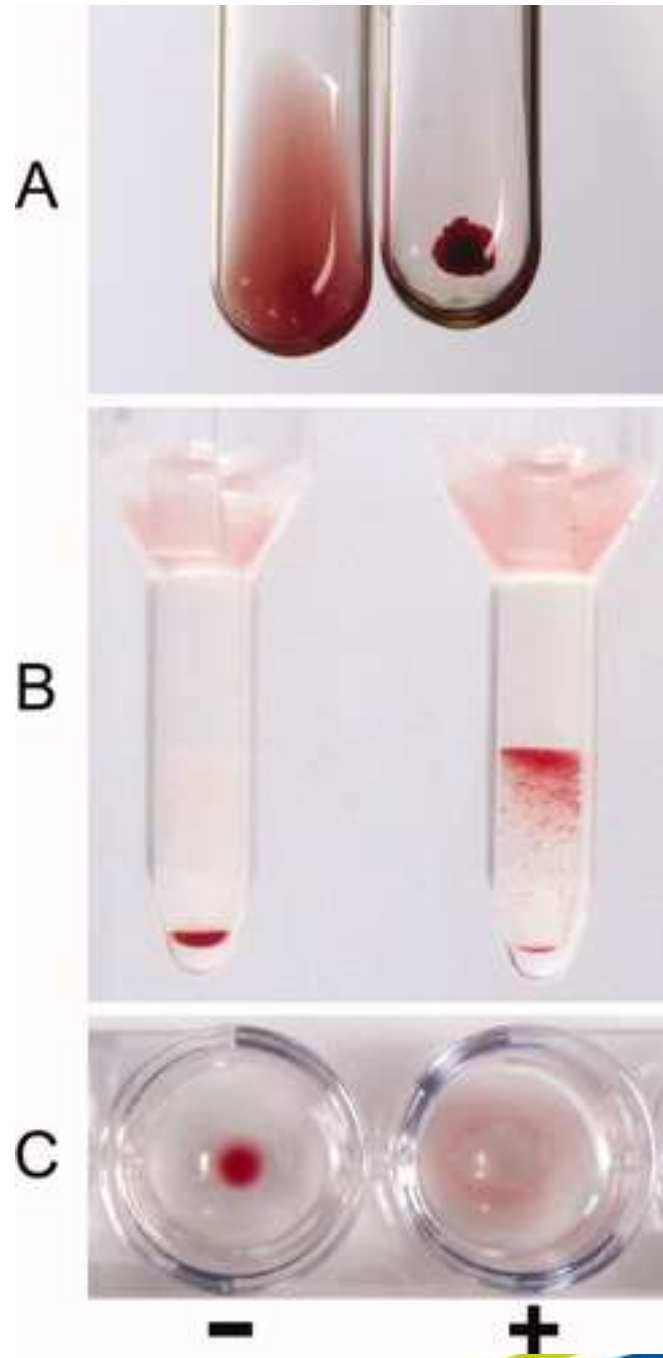


Direct Antiglobulin Test:

Goal: Detection of IgG or complement fractions bound to patient's RBCs *in vivo*



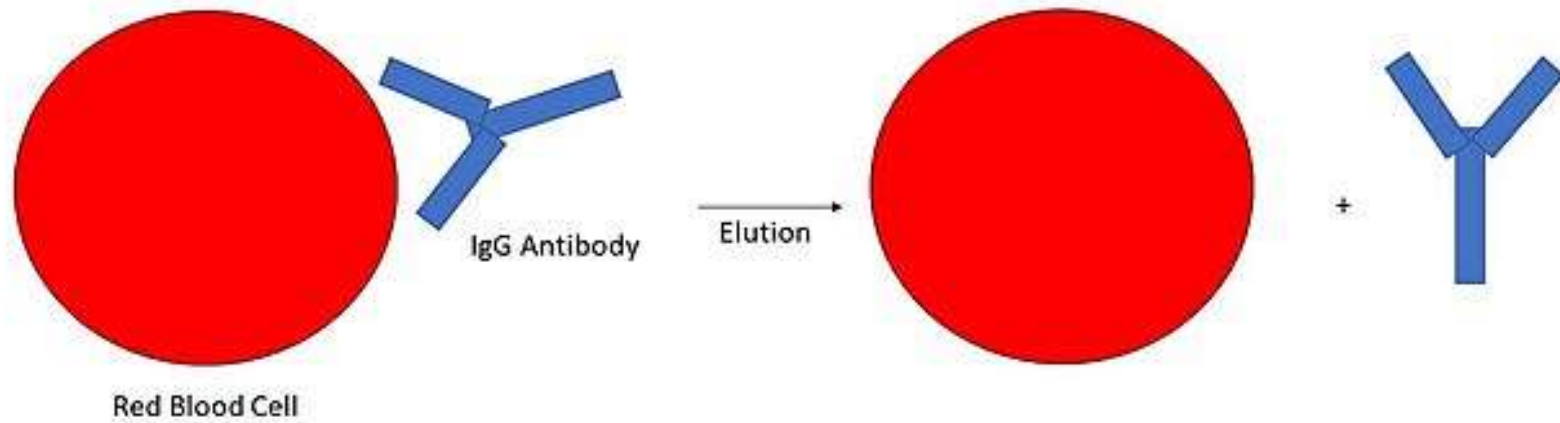




-

+

Eluate:




Treatment

- STOP TRANSFUSION!!!!
- Administer vasopressors to help increase blood pressure.
- Diuresis for renal-protective resuscitation, aiming for a urine output of ≥ 100 ml/hr:
 - Administer IV fluids for supportive therapy
 - Administer Furosemide for intrinsic renal support
- Remember to save a sample of the unit to perform your necessary DAT

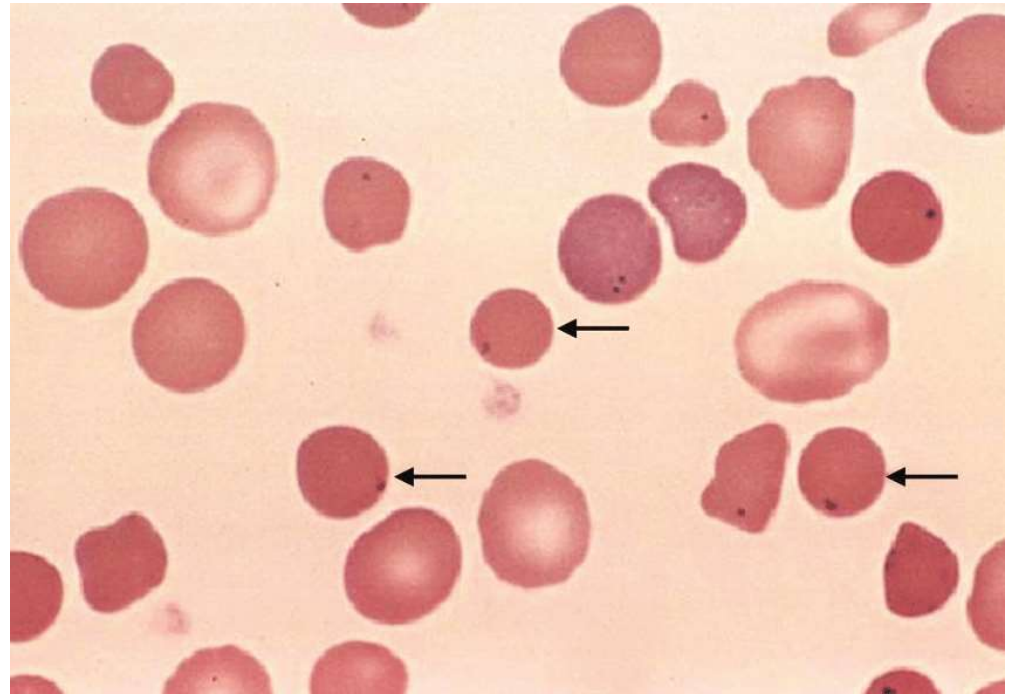
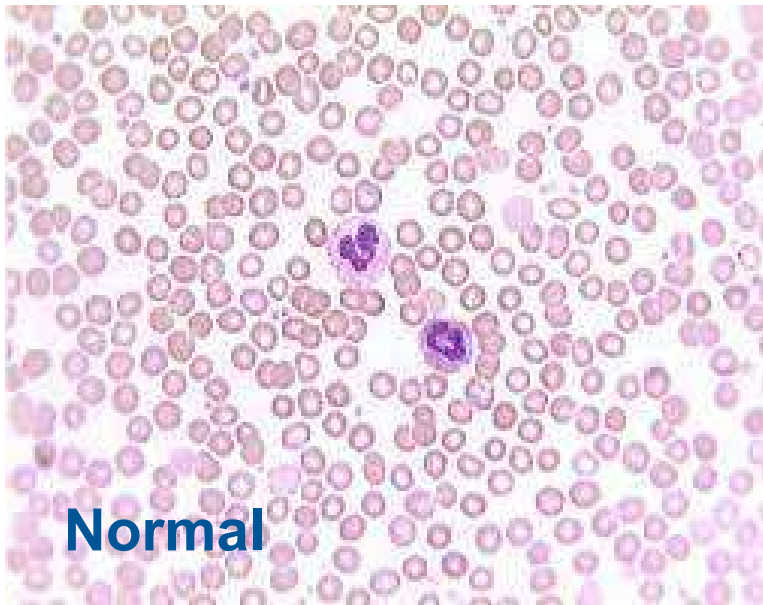
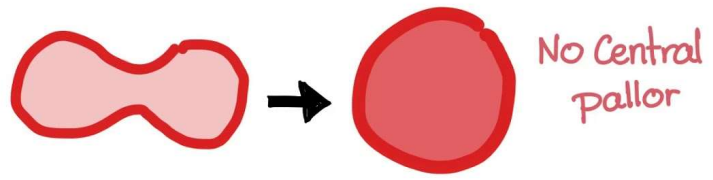
Delayed Hemolytic Transfusion Reaction

- The recipient develops antibodies to a red blood cell antigen(s) between 24 hours and 28 days after cessation of transfusion.
- Clinical signs of hemolysis are often present.
- Post-transfusion LDH and bilirubin levels increase and subsequently fall back to baseline in the following days.

What to look for:

- Positive DAT for antibodies that have developed between 24 **hours** and 28 **days** after cessation of transfusion
AND EITHER:
 - 1. Positive elution confirming an alloantibody on transfused RBC'sOR
 - 2. A newly identified red blood cell alloantibody in recipient serumOR
 - Unexplained Detection of Spherocyte's on smear
- 

SPHEROCYTES




Treatment

- Corticosteroids.
- IV immunoglobulin.
- Rituximab.
- Corresponding antigen negative blood for future transfusions.



Febrile Non-Hemolytic Transfusion Reaction (FNHTR)

- Most common cause is a reaction to passively transfused cytokines or leukocytes in the donated blood product.
 - Fever, chills or rigors without hemolysis that occurs during/within 4 hours of cessation of transfusion.
 - Cultures of the patient or the donated blood product should be negative.
 - **No laboratory evidence of acute hemolysis, (neg DAT)**
- 

Diagnosis

- Occurs during or within 4 hours of cessation of transfusion with either:
 - Fever (at least $38^{\circ}\text{C}/100.4^{\circ}\text{F}$ orally) and a change of at least $1^{\circ}\text{C}/1.8^{\circ}\text{F}$ from pre-transfusion temp
- OR**
- **Chills/rigors present alone.**



Treatment

- Stop the transfusion.
- Administer acetaminophen/ Tylenol.



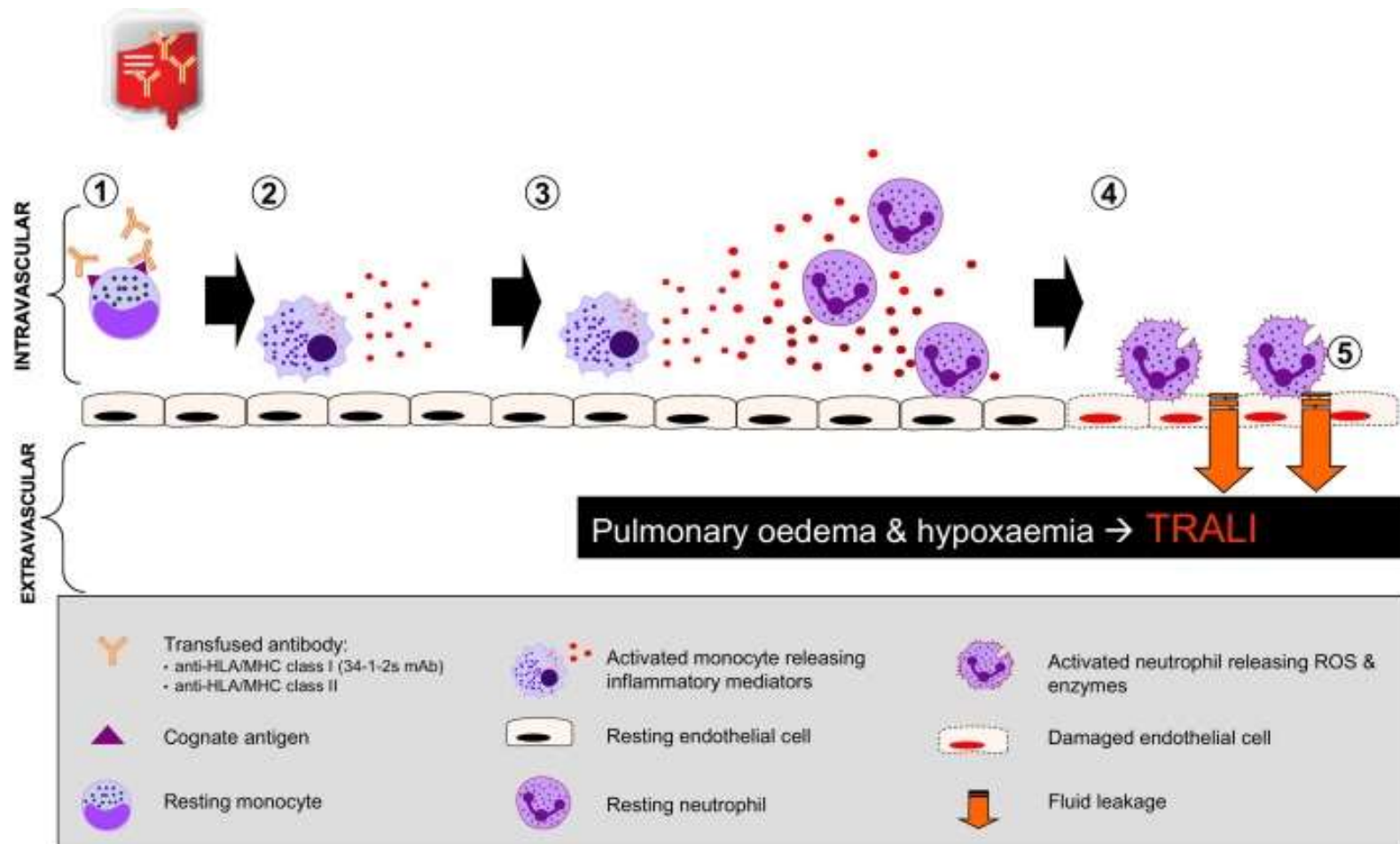
Transfusion-Related Acute Lung Injury (TRALI)

- Acute lung injury occurs within **6 hours** of cessation of transfusion.
- No evidence of acute lung injury **prior** to transfusion.


Most widely held view of the cause:

- Passively transfused HLA or HNA Ab's in donor plasma which then set off a cascade of events, leading to the attack of recipient's leukocyte Ag
- BioActive lipids suspended in plasma or storage medium of the blood product (sphingolipids found within platelet and RBC cell wall)





Things to look for:

- Hypoxemia: $\text{PaO}_2 / \text{FiO}_2$ less than or equal to 300 mmHg.
 - O_2 saturation less than 90% on room air
 - Radiographic evidence of **bilateral** pulmonary infiltrates
 - No evidence of circulatory overload (left atrial hypertension).
 - Mortality rate is 25%
- 

Bilateral Pulmonary Infiltrates

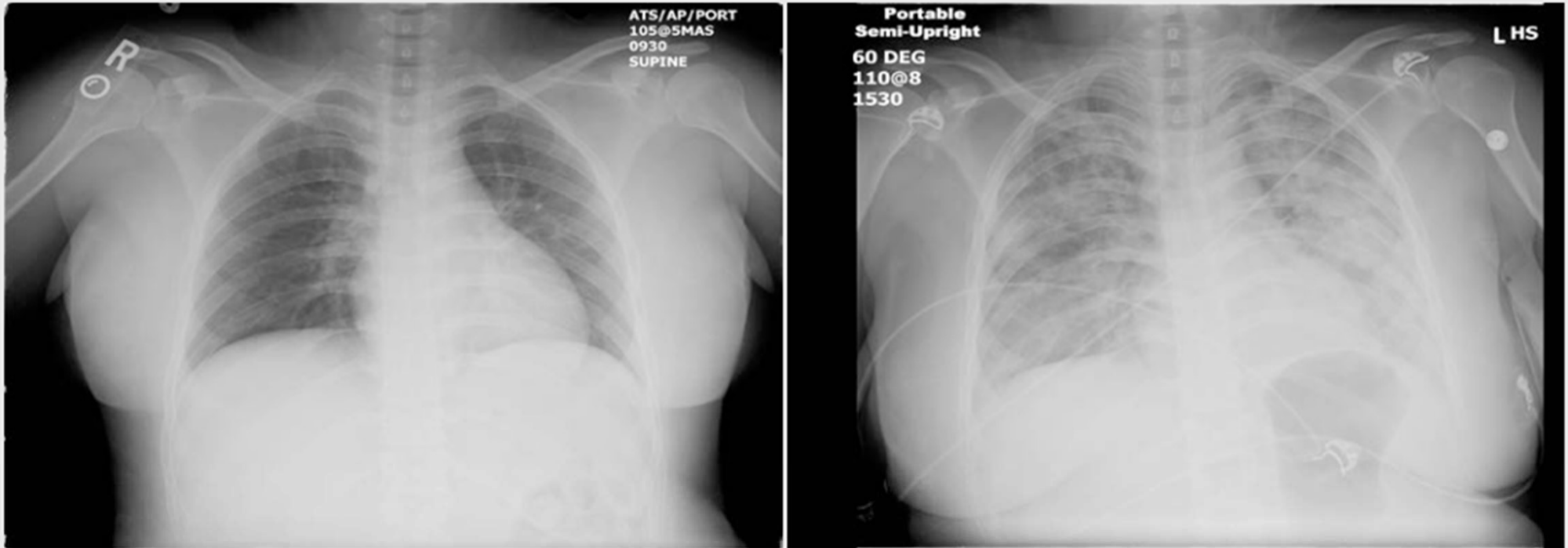



Fig 1: Pre and Post transfusion X-rays of our patient with TRALI. Bilateral Lung infiltrate with pulmonary edema is an essential criteria for the clinical diagnosis of TRALI.

Treatment


- Stop transfusion.
 - Provide respiratory and circulatory supportive care:
 - O₂ supplementation, mechanical ventilation.
 - Vasopressors if hypotensive.
- 

Transfusion-Associated Circulatory Overload (TACO)

- Occurs within 12 hours of cessation of transfusion.
- Causes: The infused volume of product cannot be processed effectively by the recipient due to:
 - High rate of infusion or high volume of infusion
 - An underlying existing cardiac or pulmonary pathology.



TACO

- Evidence of acute worsening respiratory distress:
 - You will need one of the following from A & B AND always C:
 - A. Dyspnea, cyanosis, decreased O₂ saturation values in the absence of other causes and/or
 - B. Radiographic or clinical evidence of acute worsening lung injury including:
 - Lung crackles on auscultation
 - Cough
 - Third heart sound
 - Pink sputum
 - C. Elevated BNP/NT-pro BNP (left ventricular dysfunction), elevated central venous pressure, left heart failure, fluid overload.**
- 



Cyanosis



Treatment

- Stop transfusion.
- Have patient sit up.
- Provide supplemental O₂.
- Diuretics to decrease intravascular plasma volume.
- Clinician can order volume reduced products to avoid overload complications



TRALI

- Fever
- No circulatory overload
- EF: Normal
- BNP: <250pg/ml
- Hypotension
- Edema Fluid: Exudate
- JVP unchanged
- Transient leukopenia
- Inconsistent improvement with diuretics

- Rales
- Acute Dyspnea
- Hypoxemia
- Acute Pulmonary Edema
- Diffuse B/L infiltrates

TACO

- No Fever
- Circulatory overload +
- EF: Decreased
- BNP: >1200pg/ml
- Hypertension
- Edema Fluid: Transudate
- JVP may be distended
- Leukocytes may be unchanged
- Improvement with Diuretics

TRALI vs. TACO

TRALI	TACO
<p><u>Signs & Symptoms</u></p> <ul style="list-style-type: none">•Respiratory distress•Tachypnea•Hypoxemia•Hypotension•Noncardiogenic pulmonary edema•Fever•Onset within 6 hours of transfusion <p><u>Supporting Data</u></p> <ul style="list-style-type: none">•B/L pulmonary infiltrates on CXR•Decreased WBC count•<i>Associated with HLA and/or Neutrophil Antibodies</i>	<p><u>Signs & Symptoms</u></p> <ul style="list-style-type: none">•Respiratory distress•Tachypnea•Hypoxemia•Hypertension•Cardiogenic pulmonary edema•Improves with diuretics <p><u>Supporting Data</u></p> <ul style="list-style-type: none">•B/L pulmonary infiltrates on CXR•Pretransfusion fluid overload•Elevated BNP•Increased heart size•Vascular congestion•Pulmonary wedge P > 18 mm Hg



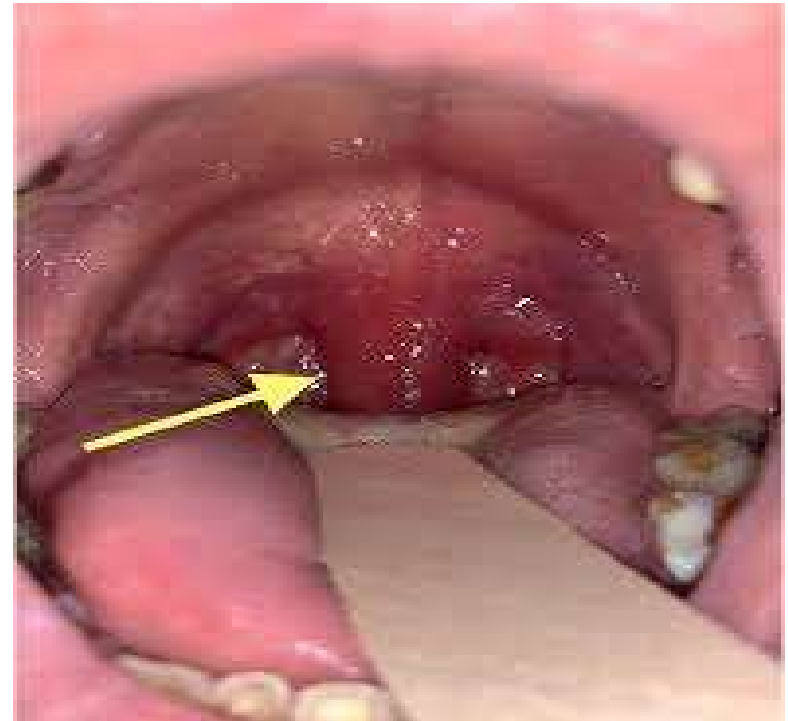
Allergic Reaction

- Occurs during or within 4 hours of the cessation of transfusion.
- It is the result of an interaction of an allergen with preformed antibodies.



Allergic Reaction

- Two or more of the following occur during or within 4 hours of cessation of transfusion:
 - Hypotension
 - Generalized flushing
 - Localized angioedema including:
 - Edema of the lips, tongue or uvula, periorbital/
conjunctival region
 - Erythema including maculopapular rash, pruritis,
urticaria
 - Respiratory distress (bronchospasm)

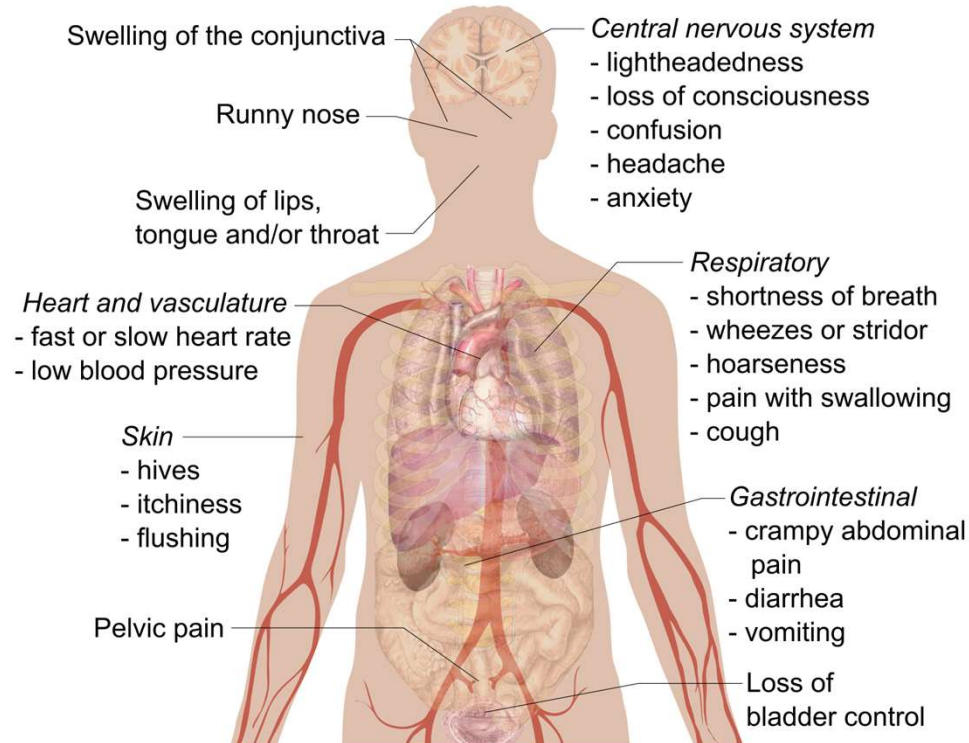


Treatment

- Stop transfusion.
- Antihistamines for hives and itching.
- Severe reactions may necessitate epinephrine, corticosteroids and respiratory support.
- Its safe to restart blood product transfusion



Anaphylactic Reaction:



Anaphylactic Reaction cont:

- Epidemiology:
 - 1 in 20,000 to 50,000 transfusions
- Mechanism:
 - Sudden, systemic release of mediators such as histamine and tryptase by mast cells and basophils
- In response to IgE or IgG mediated immune reaction

Life Threatening



Presentation:

Medical Emergency

Rapid onset- within seconds to minutes post transfusion

Shock

Hypotension

Angioedema


Wheezing

Respiratory distress


Allergic reaction symptoms



Prevention:

- Do not use the blood products from the donor who was the source of the reaction
 - Avoid plasma transfusions when there was a previous anaphylactic reaction
 - Wash the blood product (not the plasma product)
 - If patient is IgA deficient, use blood products from donor who is IgA deficient
- 

Hypotensive Transfusion Reaction

- A decline in blood pressure during or within 1 hour of cessation of transfusion.
 - Hypotension is often the **sole** manifestation.
 - Other associated symptoms may include facial flushing, dyspnea or abdominal cramping.
 - All other transfusion reactions that present with hypotension must be excluded for this diagnosis.
- 

Hypotensive Transfusion Reaction


- Adults (≥ 18 years old):
 - Drop in **systolic** blood pressure of ≥ 30 mmHg with a total systolic blood pressure \leq to 80 mmHg.
- Neonates and small infants (< 1 year old or less than 12 kg body weight):
 - Greater than 25% decline in baseline value using whichever measurement is being recorded (mean BP).
- Infants, children, and adolescents (1-18 years old):
 - Greater than 25% drop in **systolic** blood pressure from baseline.

Treatment

- Stop transfusion.
- Maintain IV access.
- Fluid bolus or vasopressors.



Transfusion Associated Dyspnea (TAD)

- Respiratory distress that occurs within 24 hours of cessation of transfusion.
 - **Does not meet criteria** for TRALI, TACO or allergic reaction.
 - Respiratory distress not explained by an underlying or pre-existing medical condition.
- 

Treatment

- Stop transfusion.
- Respiratory support as needed.



Delayed Serologic Transfusion Reaction


- Development of new clinically significant antibody against red blood cells; +DAT
- Confirmed positive direct antiglobulin test (DAT) or a positive antibody screen with a newly identified RBC alloantibody.
- **Absence of clinical signs of hemolysis**
- Demonstration of a new, clinically significant alloantibody against red blood cells between 24 hours and 28 days after cessation of transfusion despite an adequate maintained hemoglobin response.

Treatment


- Avoidance of future donated RBC Ag

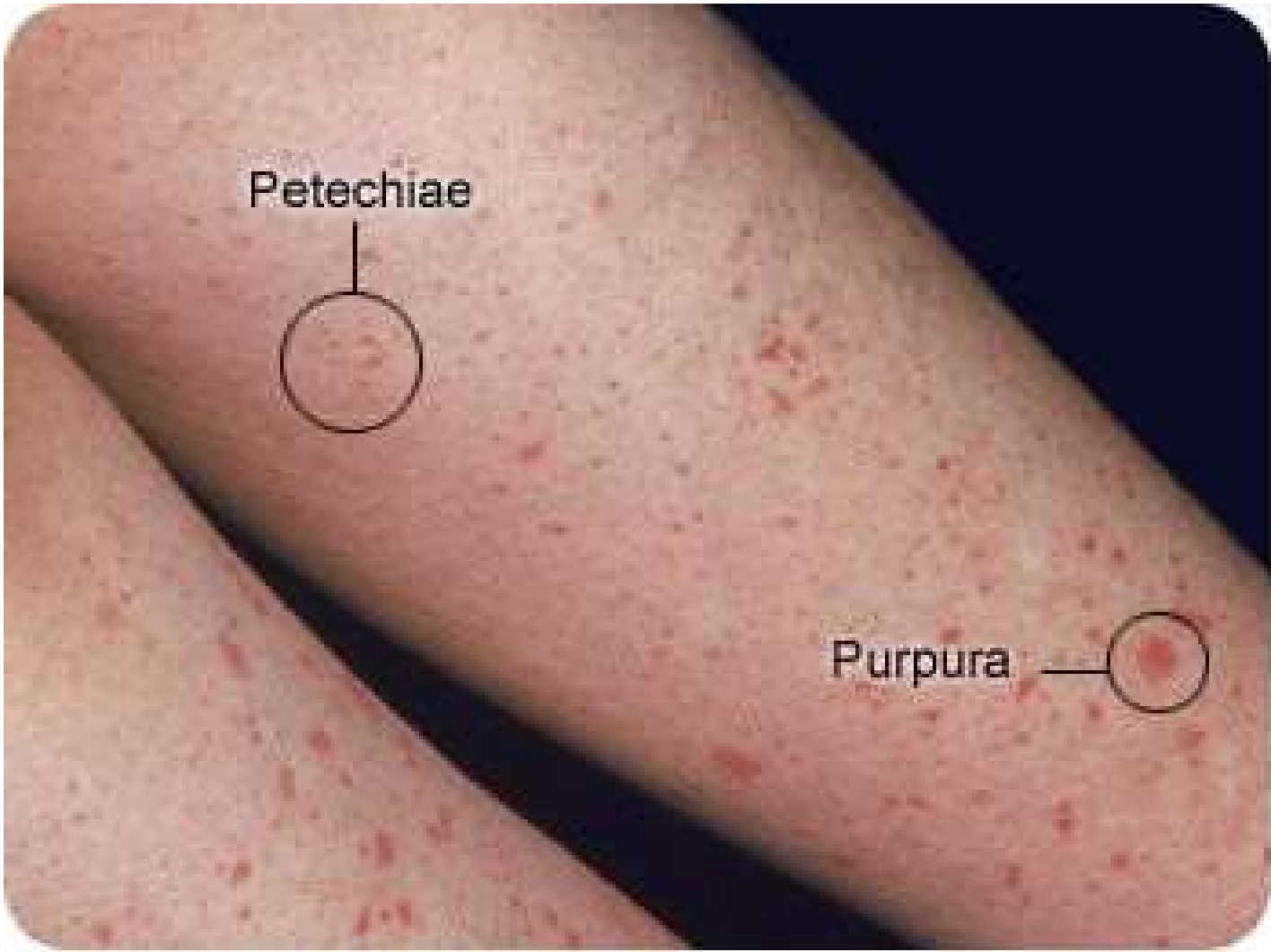


Post Transfusion Purpura

- Thrombocytopenia usually arising 5-12 days following transfusion of cellular blood components (RBC or PLT) with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system
 - Thrombocytopenia (decrease in platelet counts to less than 20% of pre-transfusion count).
 - Petechial rash
- 

Treatment:

- First line therapy is IV-Ig
 - Steroids
 - Plasmapheresis
 - Resolves usually within 2 weeks
 - Symptoms usually sudden and self-limiting
- 



Transfusion-Associated Graft vs. Host Disease (TAGVHD)

- Caused by the introduction of a blood product from an immunocompetent donor with its corresponding competent lymphocytes **into** a susceptible immunocompromised recipient.
- These competent lymphocytes engraft, proliferate and destroy host cells



Occurs within 2 days to 6 weeks after cessation of transfused product and is characterized by:

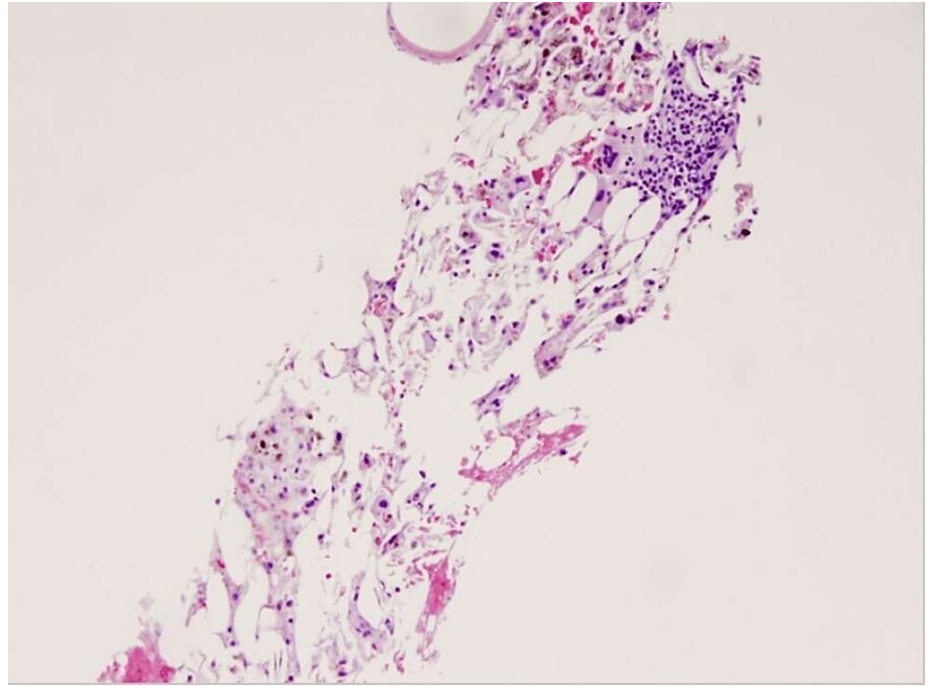
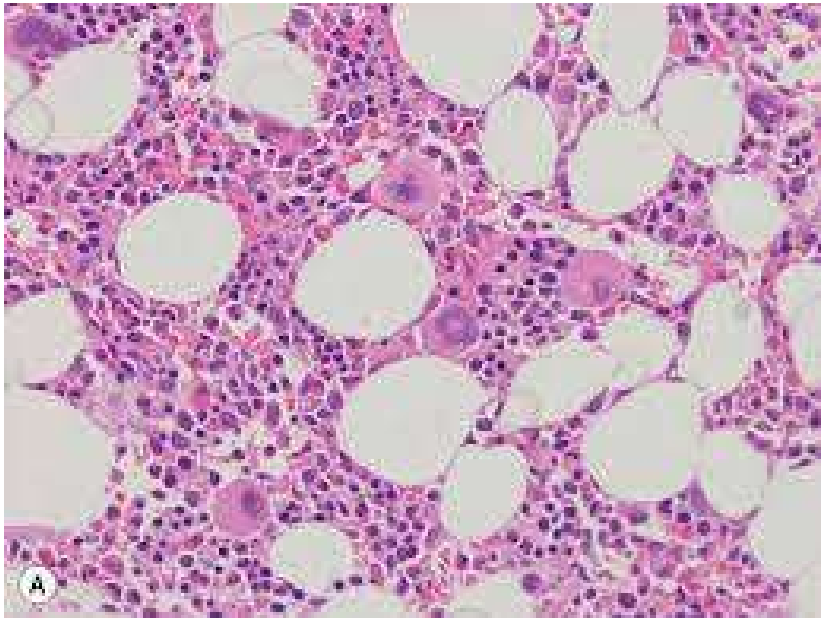
- Rash
 - Diarrhea
 - Fever
 - Hepatomegaly
 - Liver dysfunction- elevated ALT/ AST/ Bilirubin
 - Marrow dysplasia
 - Pancytopenia
- AND
- Proven characteristic histologic findings on skin and marrow biopsy



Keep in mind:

- All of our products are leuko-reduced and irradiated to avoid these issues





Treatment:

- Immunosuppressive drugs
- Bone Marrow Transplant



Transfusion Transmitted Infection

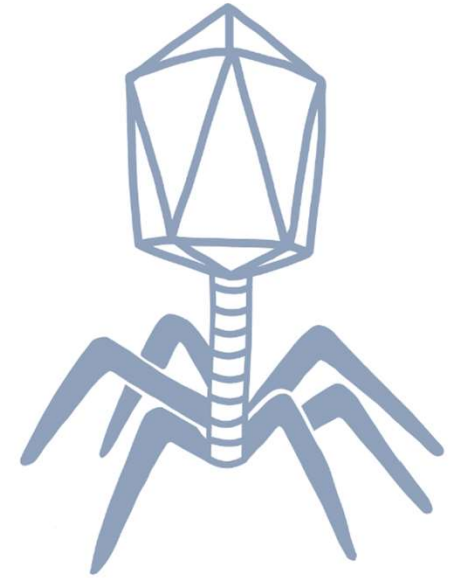
- A bacteria, virus, parasite or other potential pathogens transmitted in donated blood to the recipient.



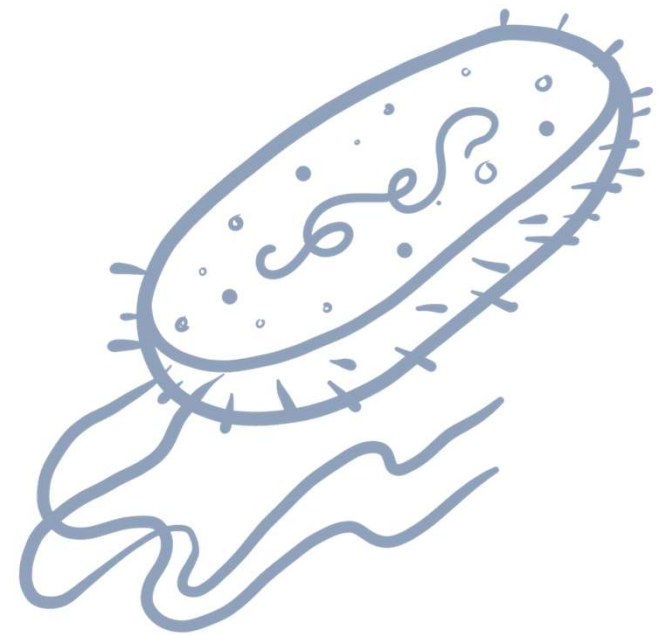
- Risk

- Viruses

- Hepatitis B virus (HBV) – one in 1 million to 1.5 million (estimated)
- Hepatitis C virus (HCV) – one in 2 million to 2.6 million (estimated)
- Human T-lymphotropic virus (HTLV) – one in 2.7 million (estimated)
- Human immunodeficiency virus (HIV) – one in 1.6 to 2.3 million (estimated)




- Risk (cont.)
 - Bacteria
 - One in 50,000 to 80,000 platelet transfusions
 - Platelets are usually stored at room temperature → greater risk of bacterial growth



Treatment

- Stop transfusion.
 - Start a broad spectrum antibiotics, then once cultures are obtained and culprit has been identified, start **specific** drug
 - Provide cardiorespiratory support.
 - Send unit to blood bank for investigation.
- 

Transfusion Reaction Key Points:

1. Acute Hemolytic Transfusion Reaction
 - Positive DAT within 24 hrs, signs of hemolysis
 2. Delayed Hemolytic Transfusion Reaction
 - 1 day to 1 month after Tx with a +DAT and hemolysis
 3. Febrile Non-Hemolytic Transfusion Reaction (FNHTR)
 - Fever/ chills /rigors, negative DAT
 4. Transfusion-Related Acute Lung Injury (TRALI)
 - Hypoxic, no prior hx, fever, bilateral lung infiltrates
 5. Transfusion-Associated Circulatory Overload (TACO)
 - Dyspnea with fluid overload picture
 6. Allergic Reactions
 - Angioedema with hypotension; respiratory distress
- 

Transfusion Reaction Key Points:

7. Hypotensive Transfusion Reaction

- Hypotension alone

8. Transfusion-Associated Dyspnea (TAD)

- Respiratory distress w/o meeting TACO and TRALI criteria

9. Delayed Serologic Transfusion Reaction

- Ab identified against RBC with a +DAT and NO HEMOLYSIS

10. Transfusion Transmitted Infection

- Fever and hypotension

11. Post Transfusion Purpura

- RASH and low platelets

12. Transfusion-Associated Graft vs. Host Disease (TAGVHD)

- Recipient is Immunocompromised whom develops hepatomegaly, marrow suppression, rash, diarrhea
- 

THANK YOU ALL FOR YOUR TIME AND ATTENTION!!!

- QUESTIONS?



References:

- Rogers M.A.M., Rohde J.M., Blumberg N. Haemovigilance of reactions associated with red blood cell transfusion: Comparison across 17 Countries. *Vox Sang.* 2016;110:266–277. doi: 10.1111/vox.12367.
- Winqvist I. Meperidine (pethidine) to control shaking chills and fever associated with non-hemolytic transfusion reactions. *Eur. J. Haematol.* 1991;47:154–155. doi: 10.1111/j.1600-0609.1991.tb00140.x.
- CDC National Healthcare Safety Network (NHSN), Blood Safety Surveillance: <https://www.cdc.gov/nhsn/acute-care-hospital/bio-hemo/index.html>
- **AABB Quick Reference Guide for NHSN Hemovigilance Module: Adverse Reaction Definitions**
- https://www.labce.com/spg1888347_cdc_classification_system_for_surveillance_of_tran.aspx
- <https://www.cdc.gov/nchs/ppt/icd9/att5romanosep08.pdf>
- Blumberg N., Heal J.M., Gettings K.F., Phipps R.P., Masel D., Refaai M.A., Kirkley S.A., Fialkow L.B. An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions. *Transfusion*

References cont.

- Semple J.W., Rebetz J., Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 2019;133:1840–1853. doi: 10.1182/blood-2018-10-860809.
- Semple J.W., McVey M.J., Kim M., Rebetz J., Kuebler W.M., Kapur R. Targeting Transfusion-Related Acute Lung Injury: The Journey From Basic Science to Novel Therapies. *Crit. Care Med*. 2018;46:e452–e458
- Ibojie J., Greiss M.A., Urbaniak S.J. Limited efficacy of universal leucodepletion in reducing the incidence of febrile nonhaemolytic reactions in red cell transfusions. *Transfus. Med*. 2002;12:181–185. doi: 10.1046/j.1365-3148.2002.00370.x