Transfusion Reactions

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LifeServe BLOOD CENTER

Your Blood. Your Hospital. Your Neighbors.

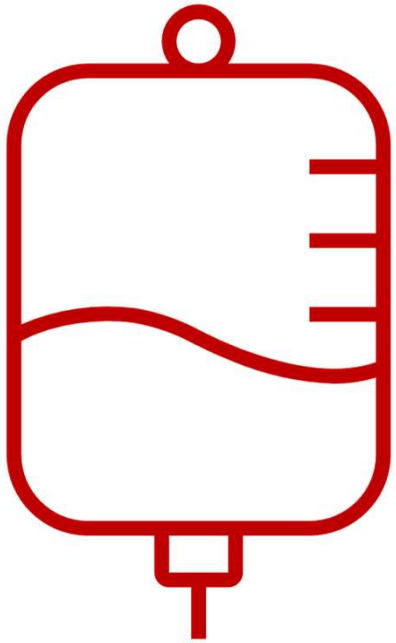
National Healthcare Safety Network
Biovigilance Component
Hemovigilance Module
Surveillance Protocol

Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf

Transfusion Reactions (TR) Covered

- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated dyspnea (TAD)
- Allergic reaction
- Hypotensive transfusion reaction
- Febrile non-hemolytic transfusion reaction (FNHTR)
- Acute hemolytic transfusion reaction (AHTR)
- Delayed hemolytic transfusion reaction (DHTR)
- Delayed serologic transfusion reaction (DSTR)
- Transfusion-transmitted infection (TTI)
- Transfusion-associated graft vs. host disease (TAGVHD)
- Post transfusion purpura (PTP)
- Other or Unknown

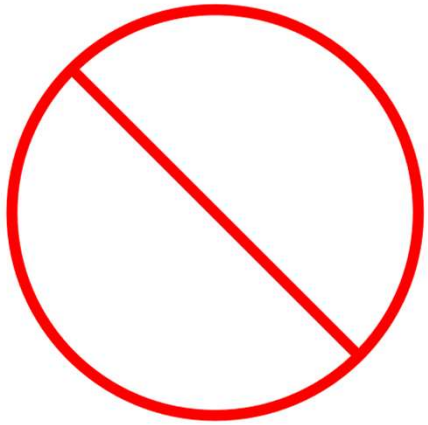


Introduction

- About 15% of hospitalized patients receive a transfusion
- If a TR is suspected
  - Immediately stop the transfusion
  - Maintain IV access with normal saline
  - Notify blood bank and physician immediately
  - Check patient identification and blood product labels
  - Monitor vital signs closely
  - Send blood samples and remaining product to blood bank
  - If needed, early consultation with hematology and ICU departments

Premedication before a transfusion

- Multiple randomized controlled trials and systematic reviews demonstrate that routine premedication with acetaminophen and antihistamines does not significantly reduce TRs
  - May be beneficial for patients with a history of severe allergic or anaphylactic transfusion reactions



CDC Criteria

1. Case definition
   - Definitive, probable, possible
2. Severity
   - Non-severe, severe, life-threatening, death, not determined
3. Imputability
   - Likelihood that the transfusion caused the reaction
   - Probable, possible, doubtful, ruled-out, not determined

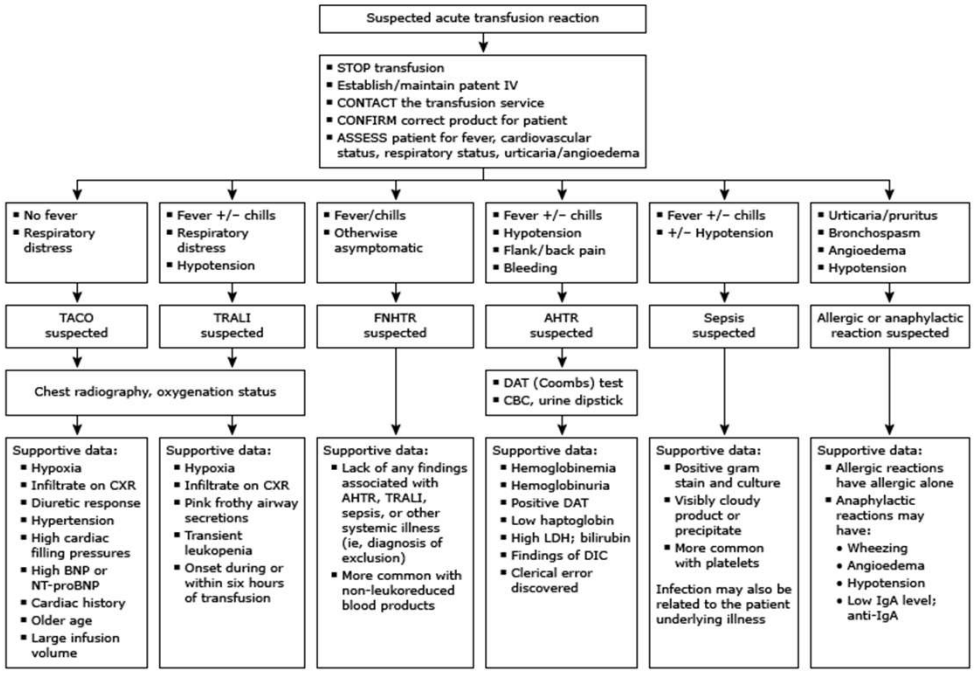
- Some categories may be listed as optional

Adverse Reaction Case Classification Criteria Tables

Transfusion-associated circulatory overload (TACO)

Case Definition	Severity	Imputability
Definitive: New onset or exacerbation of 3 or more of the following within **12 hours** of cessation of transfusion: **(At least 1 of the following:)** •Evidence of acute or worsening respiratory distress (dyspnea, tachypnoea, cyanosis and decreased oxygen saturation values in the absence of other specific causes) **and/or** •Radiographic or clinical evidence of acute or worsening pulmonary edema (crackles on lung auscultation, orthopnea, cough, a third heart sound and pinkish frothy sputum in severe cases); **or both AND** •Elevated brain natriuretic peptide (BNP) or NT-pro BNP relevant biomarker •Evidence of cardiovascular system changes not explained by underlying medical condition (Elevated central venous pressure, evidence of left heart failure including development of tachycardia, hypertension, widened pulse pressure, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema) •Evidence of fluid overload **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanations for circulatory overload are possible. **Probable:** Transfusion is a likely contributor to circulatory overload **AND EITHER** The patient received other fluids as well **OR** The patient has a history of cardiac insufficiency that could explain the circulatory overload, but transfusion is just as likely to have caused the circulatory overload. **Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains circulatory overload. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Initial approach to a suspected acute transfusion reaction



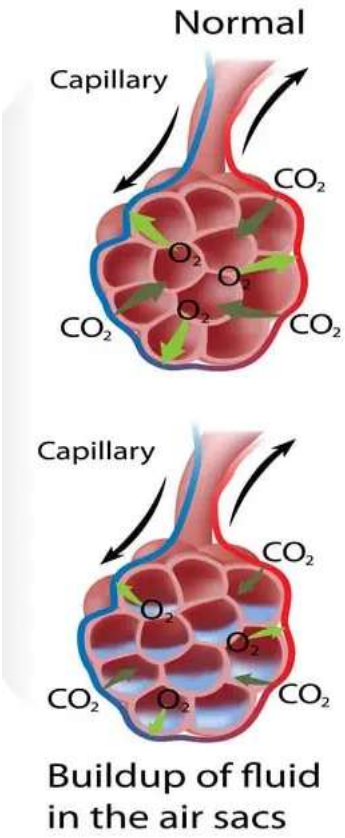
These are some of the most common and life-threatening reactions; other reactions are also possible and should be pursued if the clinical picture seems inconsistent with one of these.

- The transfusion service should be notified of any severe transfusion reaction and may request samples of the transfused product and patient blood.
- The transfused product should not be discarded until discussion with the transfusion service has taken place.
- In cases of suspected AHTR due to ABO mismatch, the transfusion service must be contacted immediately because another patient may be at risk of receiving the incorrect blood product (if two products were accidentally interchanged).
- Any patient with a potentially serious reaction and/or unstable vital signs who is not currently at an acute care facility should be transferred to an acute care facility or an acute care environment at the current facility.
- Refer to UpToDate topics on transfusion reactions for further details of the evaluation and management of these conditions.

IV: intravenous line; TACO: transfusion-associated circulatory overload; TRALI: transfusion-related acute lung injury; FNHTR: febrile nonhemolytic transfusion reaction; AHTR: acute hemolytic transfusion reaction; DAT: direct antiglobulin test (Coombs test); CBC: complete blood count; CXR: chest x-ray; NT-proBNP: N-terminal pro-(brain natriuretic peptide); LDH: lactate dehydrogenase; DIC: disseminated intravascular coagulation; IgA: immunoglobulin A.

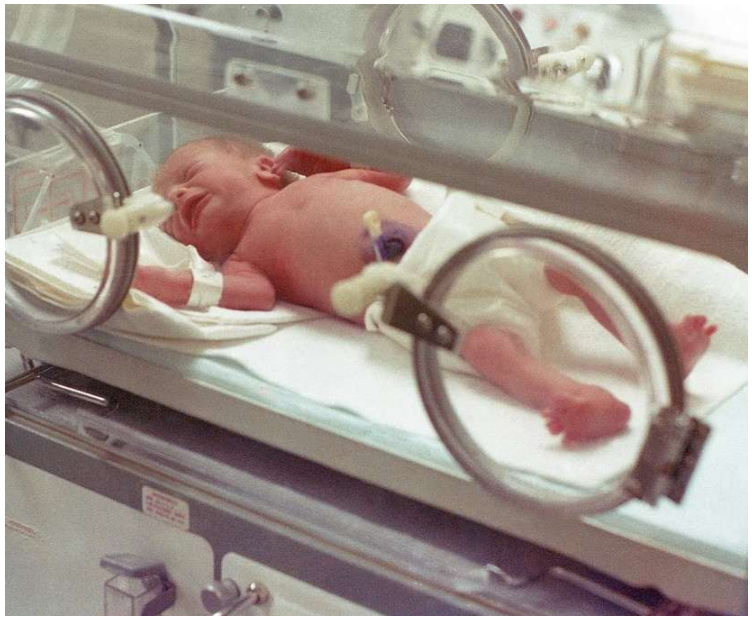
Transfusion-associated circulatory overload (TACO)

- Pulmonary edema due to volume excess or circulatory overload
- When patients receive a large volume of a transfused product over a short period of time
- Can occur with blood component
- Leading cause of transfusion-related mortality



TACO

- Risk factors
  - Pre-existing cardiac and/or kidney dysfunction
  - Small stature, low body weight, extremes of age (<3 years, >60 years), hypoalbuminemia
  - History of heart failure
  - Female
  - History of chronic pulmonary disease
  - Higher rate and volume of transfusion
    - Rarely seen with MTP

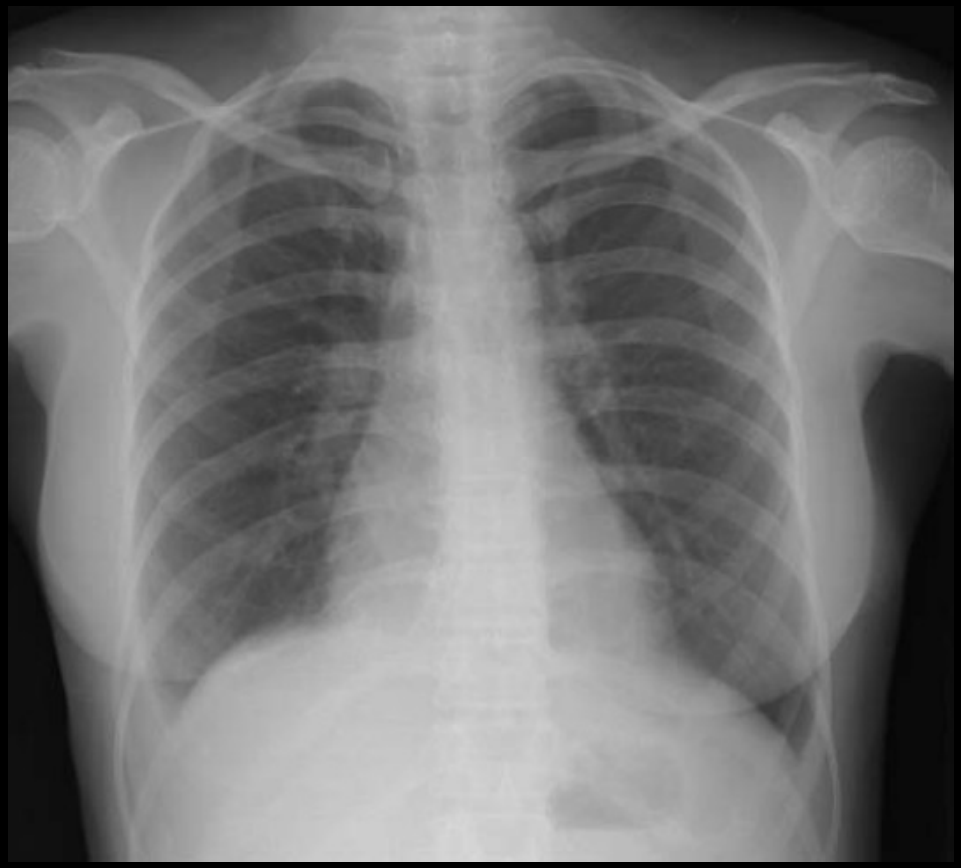


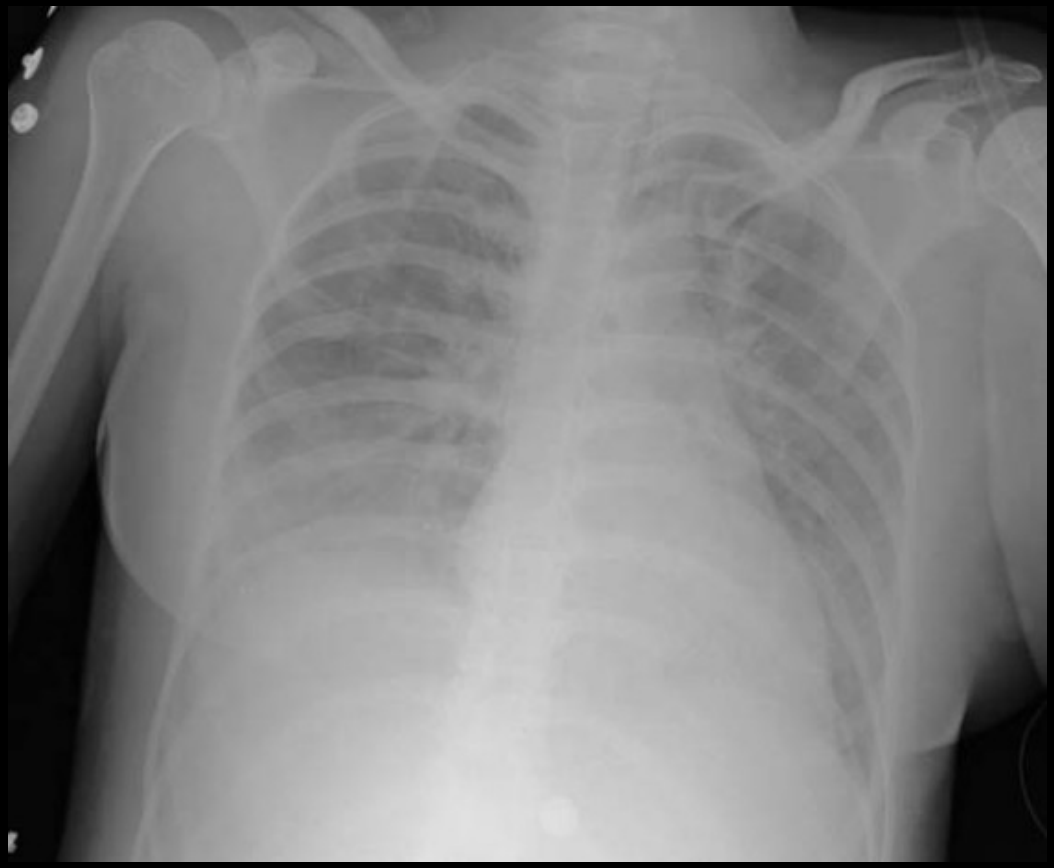
TACO

- Incidence
  - ~ 1% of transfusions
  - True frequency difficult to assess → lack of a highly sensitive and specific clinical parameter or laboratory test
  - Under-reporting → as mild respiratory distress that resolves with diuresis may not be reported
  - Higher in hospitalized patients, especially ICU

TACO

- Case definition → definitive
  - New onset or exacerbation of 3 or more of the following within 12 hours of cessation of transfusion:
    - Evidence of acute or worsening respiratory distress (dyspnea, tachypnoea, cyanosis and decreased oxygen saturation values in the absence of other specific causes) and/or
    - Radiographic or clinical evidence of acute or worsening pulmonary edema (crackles on lung auscultation, orthopnea, cough, a third heart sound and pinkish frothy sputum in severe cases); or both
  - AND
    - Elevated brain natriuretic peptide (BNP) or NT-pro BNP
    - Evidence of cardiovascular system changes not explained by underlying medical condition (elevated central venous pressure, evidence of left heart failure including development of tachycardia, hypertension, widened pulse pressure, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema)
    - Evidence of fluid overload





TACO

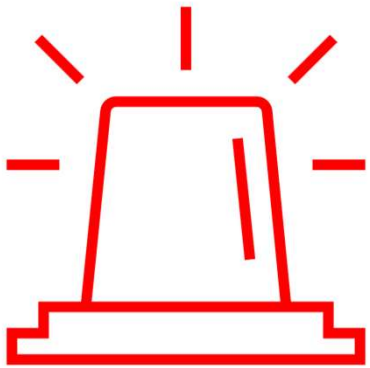
- Management
  - Fluid mobilization, supplementary oxygen; assisted ventilation if needed
  - Do not delay interventions to stabilize the patient and provide adequate oxygenation while performing additional evaluations or confirming the diagnosis

TACO

- Prevention
  - Avoid unnecessary transfusions
    - Transfuse appropriate number of units, e.g. one and then recheck values
  - Avoid rapid transfusion
    - 2.0 to 2.5 mL/kg for routine patients
    - 1 mL/kg per hour if as risk of overload
  - Reduce the volume of blood products
    - RBCs can be centrifuged and concentrated
    - Split into two units
  - Diuretics during the transfusion

Transfusion-Related Acute Lung Injury (TRALI)

- A serious and potentially fatal complication of transfusion in which a patient develops rapid lung injury and noncardiogenic pulmonary edema due to activation of immune cells in the lungs
- Can be life-threatening
- Understanding of its pathophysiology and diagnostic criteria continue to evolve



TRALI

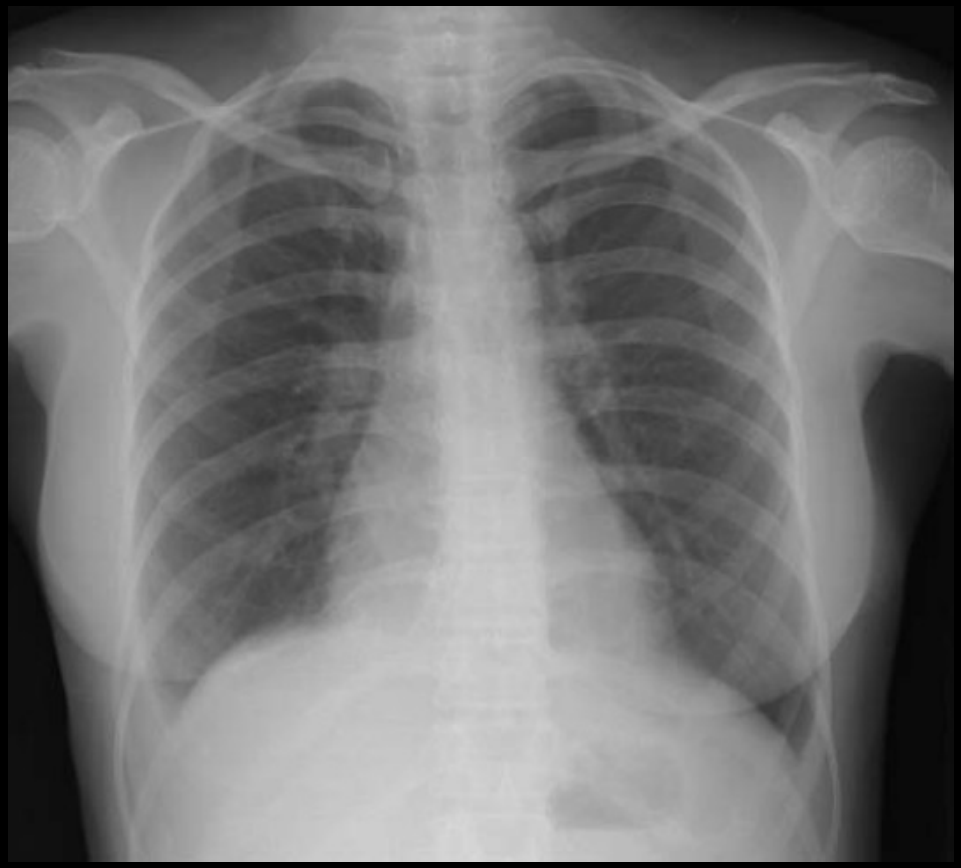
- Pathogenesis → two-hit mechanism
  1. Neutrophil sequestration and priming
     - **Sequestration**: neutrophils accumulate in the lung vasculature due to recipient factors such as endothelial injury
     - **Priming**: shifting of neutrophils to a state where they will respond to an otherwise innocuous signal
  2. Neutrophil activation
     - Activation of neutrophils by a factor in the blood product
       - Biologic response modifiers
       - HLA antibodies
       - HNA antibodies
     - Release of cytokines, reactive oxygen species, oxidases, and proteases that damage the pulmonary capillary endothelium

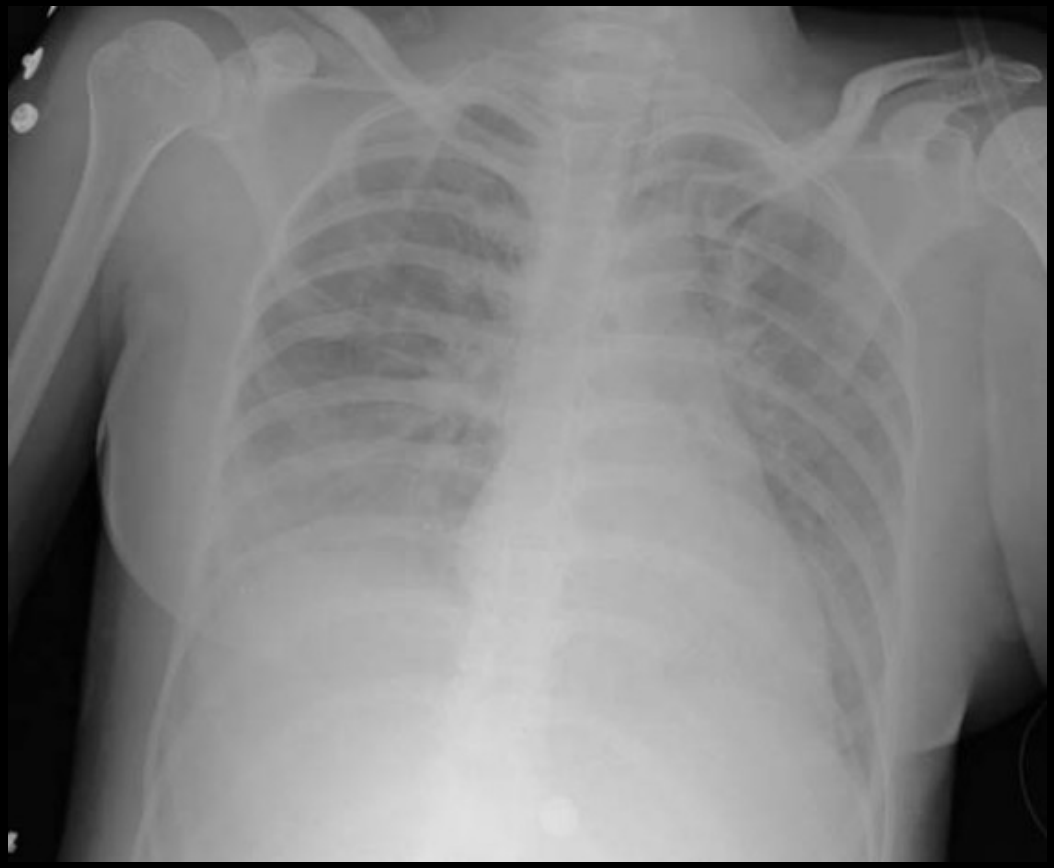
TRALI

- Risk factors
  - Recent surgery, cytokine treatment, massive blood transfusion, active infection
  - Critically ill patients, especially those with evidence of systemic inflammation

TRALI

- Case definition → definitive
  - NO evidence of acute lung injury (ALI) prior to transfusion
    - AND
  - ALI onset during or within 6 hours of cessation of transfusion
    - AND
  - Hypoxemia defined by any of these methods:
    - PaO2/FiO2 less than or equal to 300 mm Hg
    - Oxygen saturation less than 90% on room air
    - Other clinical evidence
  - AND
    - Radiographic evidence of bilateral infiltrates
  - AND
    - No evidence of left atrial hypertension (i.e., circulatory overload)





TRALI

- Treatment
  - Fluid resuscitation and/or vasoactive support if needed
  - Ventilator if needed
- Mortality
  - Varies according to the patient population
  - Critically ill → higher risk
- Prevention
  - Collect plasma from donors who are least likely to have HLA antibodies → males, females never pregnant

Transfusion-Associated Dyspnea (TAD)

- Diagnosis of exclusion
  - Acute respiratory distress occurring within 24 hours of transfusion that does not meet criteria for TRALI, TACO, or allergic TR
- Treatment
  - Supportive
  - Manage respiratory symptoms, e.g. oxygen

TAD

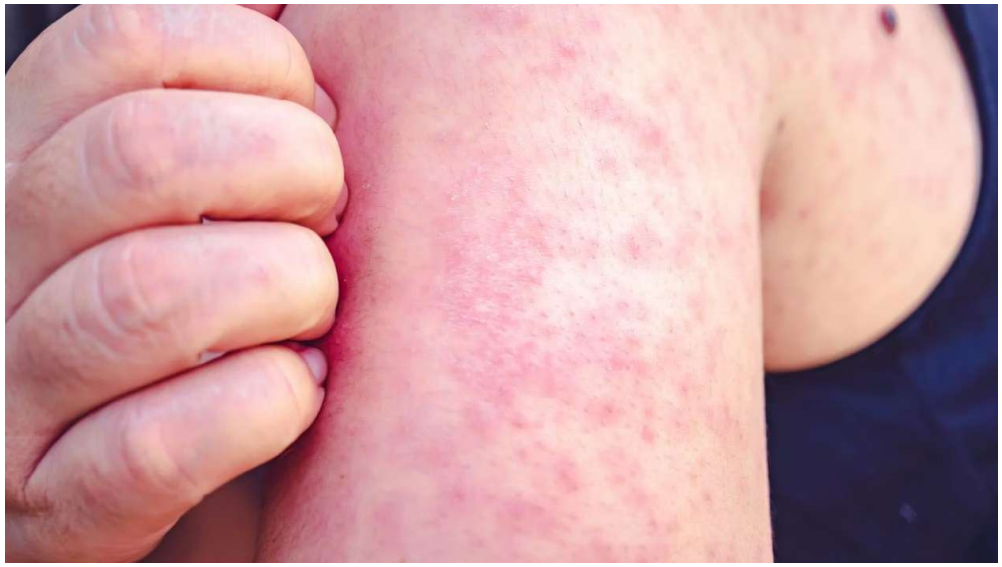
- Generally, not associated with high mortality rates compared to other TRs
  - Significant, often under-reported complication
- Relatively new classification
  - Exact mechanism not fully understood
    - “Mild" or "incomplete" version of TRALI or TACO?
    - Unique inflammatory response to biological components in transfused product?

TAD

- Case definition → definitive
  - Acute respiratory distress occurring within 24 hours of cessation of transfusion
    - AND
  - Allergic reaction, TACO, and TRALI definitions are not applicable

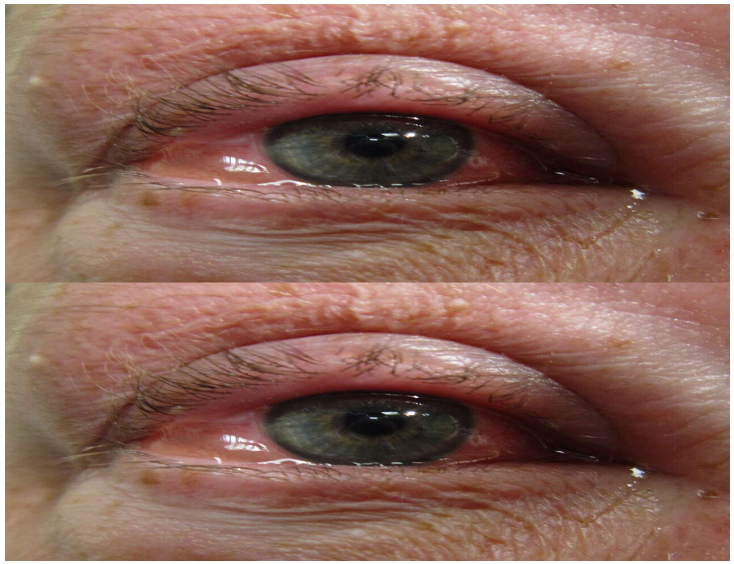
Allergic TR

- Most often associated with itching and hives
- Can be due to both recipient predisposition to allergic reactions and donor factors



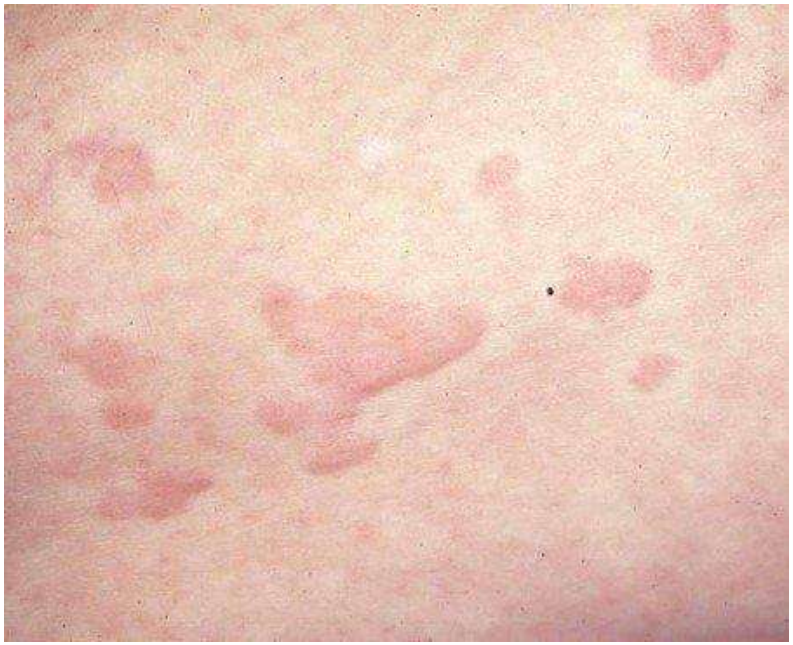
Allergic TR

- Case definition → definitive
  - 2 or more of the following occurring during or within 4 hours of cessation of transfusion
    - Conjunctival edema
    - Edema of lips, tongue and uvula
    - Erythema and edema of the periorbital area
    - Generalized flushing
    - Hypotension
    - Localized angioedema
    - Maculopapular rash
    - Pruritus
    - Respiratory distress; bronchospasm
    - Urticaria



Allergic TR

- 1 to 3% of transfusions; more likely with plasma and platelets
- Hives, pruritus
- Lab testing not required as long as no as angioedema, wheezing, or hypotension



Allergic TR

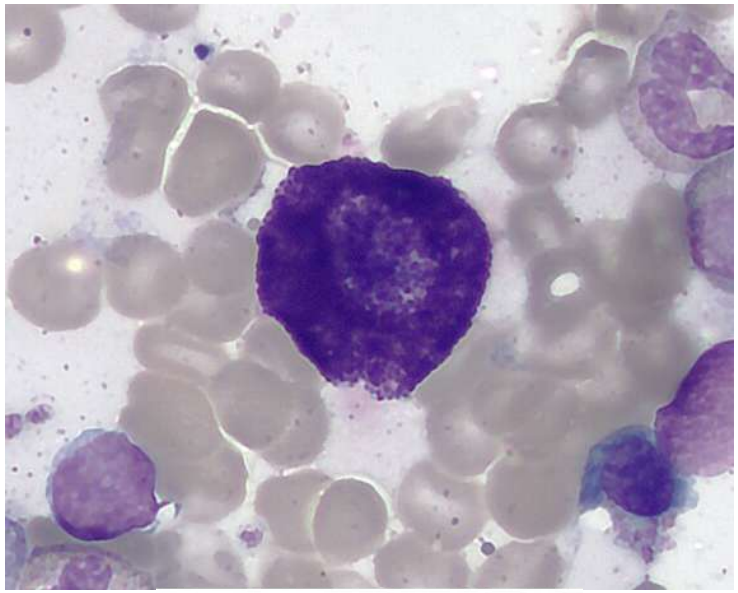
- Treatment
  - Pause the transfusion
  - Diphenhydramine
    - Oral or IV
    - 25 to 50 mg → additional dose if needed
  - More severe allergic reactions or those refractory to diphenhydramine
    - 20 mg famotidine IV
    - 50 mg hydroxyzine PO
    - 25 mg methylprednisolone IV

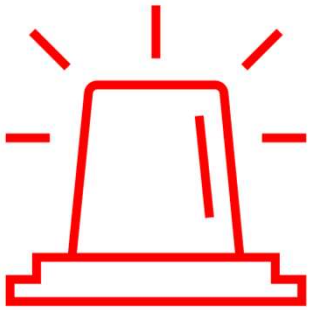
Allergic TR

- Can restart the transfusion with the same unit
  - After 15 to 30 minutes, and
  - Additional allergic symptoms are not developing
- If the patient develops more severe allergic symptoms, such as wheezing, angioedema, or hypotension…
  - Discontinue the transfusion immediately
  - Additional interventions to treat anaphylaxis → next topic

Anaphylactic TR

- No CDC criteria
- 1 in 20,000 to 50,000 transfusions
- Due to sudden, typically massive systemic release of mediators → histamine and tryptase by mast cells and basophils
  - Typically, in response to an immunoglobulin-mediated immune reaction, often mediated by IgE or IgG
- Can occur with any product
- A medical emergency



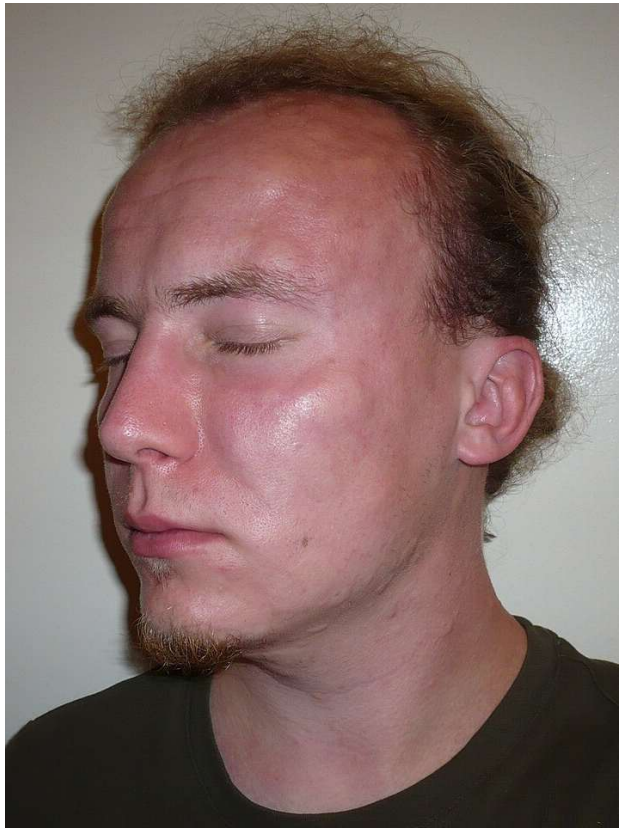


Anaphylactic TR

- IgA deficiency
  - Patient is transfused and develops an antibody against IgA
  - During the next transfusion, the IgA antibody reacts with the IgA in the transfused product
  - Usually in patients with complete absence of IgA
  - Even then, only about 1 in 1500 develop anti-IgA

Anaphylactic TR

- Presentation
  - Seconds to minutes of transfusion initiation
    - Shock
    - Hypotension
    - Angioedema
    - Respiratory distress
    - Wheezing
  - May or not be preceded or accompanied by allergic reaction symptoms → pruritus, urticaria, flushing



Acute management:
The first and most important treatment in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis. Epinephrine is given immediately upon recognition of anaphylaxis.
Airway – Early intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.
Monitoring – Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed.
Promptly and simultaneously, give:
IM epinephrine (1 mg/mL preparation) – Give epinephrine 0.3 to 0.5 mg IM in the mid-outer thigh. Can repeat every 5 minutes (or more frequently), as needed. If epinephrine is injected promptly IM, most patients respond to 1, 2, or at most, 3 doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (refer to below).
If hypotensive, place patient in recumbent position, if tolerated, and elevate lower extremities.
Oxygen – Give with nonrebreather mask at 15 liters/minute flow rate or commercial high-flow oxygen masks (providing at least 70% and up to 100% oxygen), as needed.
Crystalloid (eg, Ringer's lactate or normal saline) rapid bolus – Establish two large-bore IV lines. Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur. Monitor urine output.
Albuterol – For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer, or 2 to 3 puffs by metered dose inhaler. Repeat, as needed.
Adjunctive therapies (for residual symptoms after adequate response to epinephrine):
H1 antihistamine* **–** For residual itching or urticaria, give cetirizine (preferred) 10 mg IV (given over 2 minutes) or diphenhydramine 25 to 50 mg IV (given over 5 minutes).
H2 antihistamine* **–** For residual itching or urticaria, may give famotidine 20 mg IV (given over 2 minutes).
Glucocorticoid* **–** For residual bronchospasm and for patients requiring more than 2 doses of IM epinephrine or IV epinephrine, give methylprednisolone 80 to 125 mg IV or prednisone 40 to 60 mg orally.

Treatment of refractory symptoms:
Epinephrine infusion[¶] **–** For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at **0.1 microgram/kg/minute** by infusion pump[Δ]. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.
Vasopressors[¶] **–** Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure and cardiac rate/function and oxygenation monitored by pulse oximetry.
Glucagon – Patients on beta blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 micrograms/minute. Rapid administration of glucagon can cause vomiting.
Methylene blue – Single bolus of 1 to 2 mg/kg given over 20 to 60 minutes may improve vasoplegia.
Extracorporeal membrane oxygenation (ECMO) – Early consultation with ECMO team, if available, for patients unresponsive to complete resuscitative efforts.

Instructions on how to prepare and administer epinephrine for IV continuous infusions are available as separate tables in UpToDate.

IM: intramuscular; IV: intravenous.

* These medications should not be used as initial or sole treatment.

¶ All patients receiving an infusion of epinephrine and another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation.

Δ For example, the initial infusion rate for a 70 kg patient would be 7 micrograms/minute. This is consistent with the recommended range for non-weight-based dosing for adults, which is 2 to 10 micrograms/minute. Non-weight-based dosing can be used if the patient's weight is not known and cannot be estimated.

Adapted from: Simons FER. Anaphylaxis. J Allergy Clin Immunol 2010; 125:S161.

Graphic 58346 Version 37.0

Anaphylactic TR

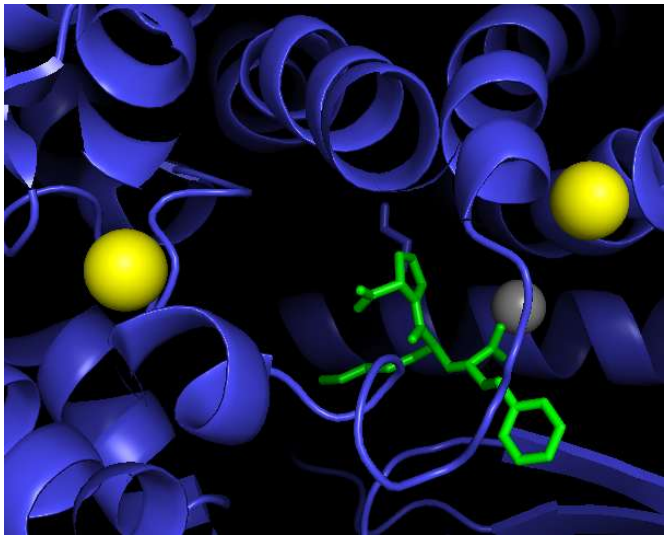
- Prevention
  - Establishing the diagnosis after the fact and avoiding future exposures
  - Avoid plasma transfusion in individuals with a previous anaphylactic TR
  - Wash RBCs and platelets
  - Blood products from IgA-deficient donors

Hypotensive TR

- Diagnosis of exclusion
- Drop in BP without other causes of hypotension
  - Systolic BP decreases by 30 mmHg or more, may fall to < 80 mmHg within one hour
  - Generally, within the first 10 to 15 minutes of transfusion initiation
  - Returns to baseline once the transfusion is stopped
- Other TRs with hypotension (e.g. TRALI, anaphylaxis, acute hemolytic, TTI) and underlying disease ruled out

Hypotensive TR

- Most common with platelet transfusion
- During therapeutic apheresis and in patients on extracorporeal circuits
- Patient taking an ACEi
  - Mechanism is thought to involve vasoactive kinins, e.g. bradykinin
- Reactions are rapidly reversible
  - IV saline bolus
- Stop ACEi for at least 24 hours before therapeutic apheresis
  - Often times switched to another BP med

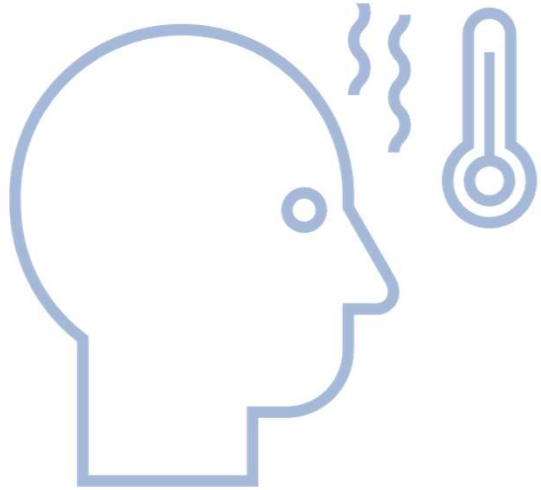


Hypotensive TR

- Case definition → definitive
  - All other adverse reactions presenting with hypotension are excluded
    - AND
  - Hypotension occurs during or within 1 hour after cessation of transfusion
  - Adults (18 years and older)
    - Drop in systolic BP of greater than or equal to 30 mmHg and systolic BP less than or equal to 80 mmHg
  - Infants, children and adolescents (1 year to less than 18 years old)
    - Greater than 25% drop in systolic BP from baseline (e.g. drop in systolic BP of 120 mmHg to below 90 mmHg)
  - Neonates and small infants (less than 1 year old OR any age and less than 12 kg body weight)
    - Greater than 25% drop in baseline value using whichever measurement is being recorded (e.g., mean BP)

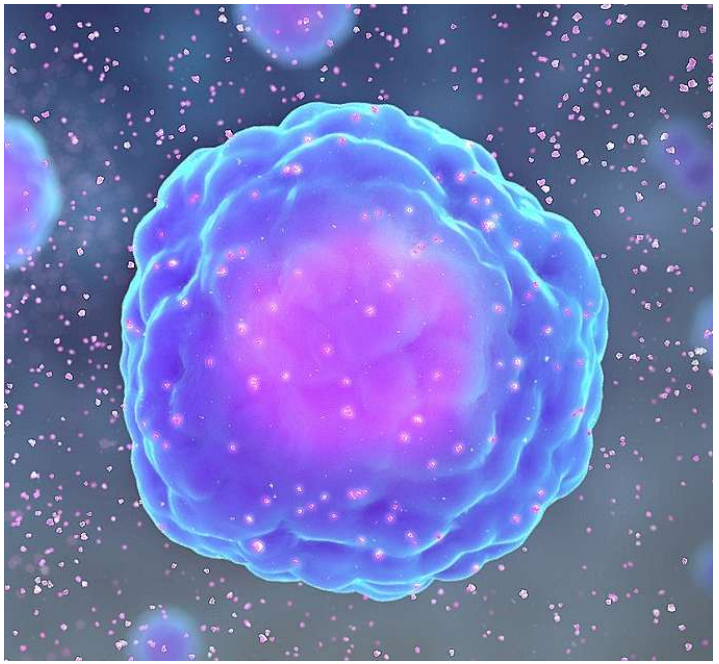
Febrile XR

- Most common TR → 1% of transfusions
- Benign
  - Can be discomforting for the patient
- Can be expensive
  - Requires that an infectious etiology be excluded
  - Often an additional unit of blood is crossmatched and transfused



Febrile XR

- Risk factors
  - Can occur with any product
  - More frequent in children
  - 40% will experience a subsequent febrile reaction
    - 45% with the next transfusion
- Mechanism
  - Mediated by donor leukocytes and/or accumulation of cytokines in the blood product



Febrile XR

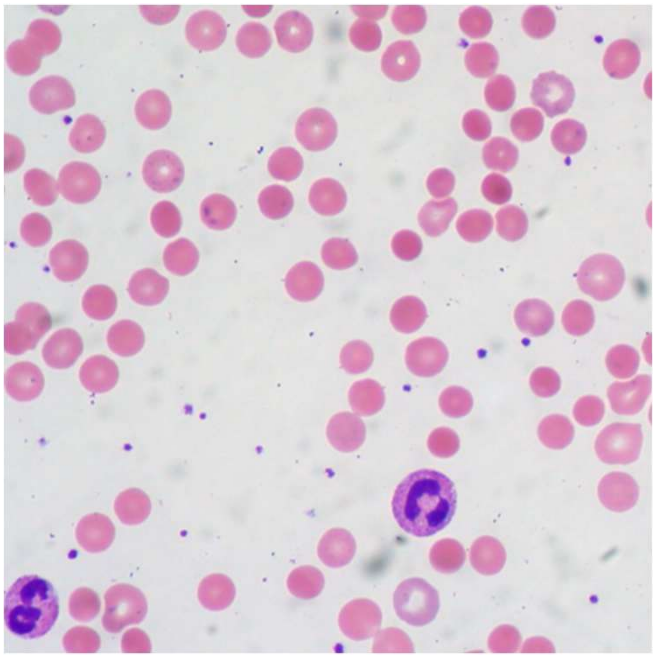
- Case definition → definitive
  - Occurs during or within 4 hours of cessation of transfusion
    - AND EITHER
  - Fever (greater than or equal to 38°C/100.4°F oral and a change of at least 1°C/1.8°F) from pre-transfusion value
    - OR
  - Chills/rigors are present

Febrile XR

- Management
  - Antipyretics for fever
  - Meperidine for severe rigors
- Prevention
  - Leukoreduction of blood products
    - All blood products are leukoreduced

Acute Hemolytic XR

- Intravascular hemolysis mediated by preformed RBC antibodies
  - From a previous transfusion, pregnancy
- Classic triad: fever, flank pain, pink to red urine
- Fever or chills
  - 80% of cases
  - May be the only symptom
- Patients may report a "sense of impending doom”
- Severity → antibody titer, volume transfused, transfusion rate



Occurs during, or within 24 hours of cessation of transfusion with new onset of **ANY** of the following signs/symptoms:

- Back/flank pain
- Chills/rigors
- Disseminated intravascular coagulation (DIC)
- Epistaxis
- Fever
- Hematuria (gross visual hemolysis)
- Hypotension
- Oliguria/anuria
- Pain and/or oozing at IV site
- Renal failure

AND

2 or more of the following:

- Decreased fibrinogen
- Decreased haptoglobin
- Elevated bilirubin
- Elevated LDH
- Hemoglobinemia
- Hemoglobinuria
- Plasma discoloration c/w hemolysis
- Spherocytes on blood film

AND EITHER

(IMMUNE-MEDIATED)

Positive direct antiglobulin test (DAT) for anti-IgG or anti-C3

AND

Positive elution test with alloantibody present on the transfused red blood cells

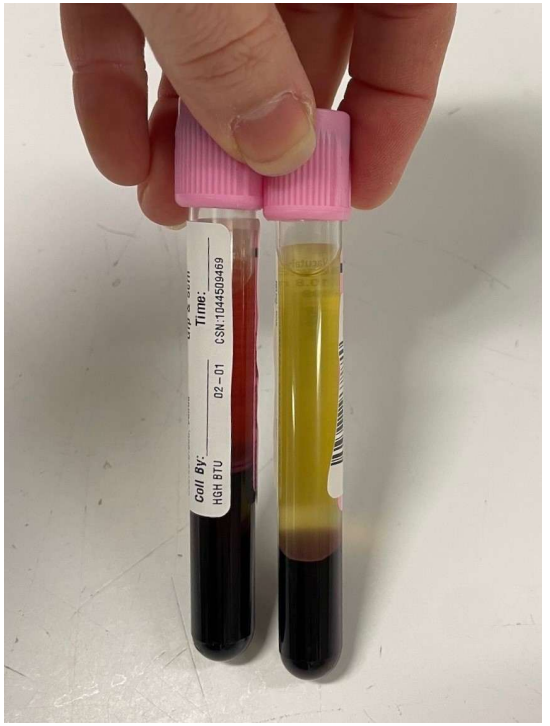
OR

(NON-IMMUNE MEDIATED)

Serologic testing is negative, and physical cause (e.g., thermal, osmotic, mechanical, chemical) is confirmed.

Acute Hemolytic XR

- Lab testing
  - Use the arm opposite the product was transfused. If not possible, use a separate site on the same arm.
  - Inspect serum for hemolysis → pink or dark brown
  - Repeat ABO compatibility
  - Additional antibody studies if ABO incompatibility is excluded
  - Repeat crossmatch
  - Direct antiglobulin test (DAT, aka Coombs)
  - Urinalysis
  - Free hemoglobin
  - Hemolysis testing → haptoglobin, LDH, unconjugated (indirect) bilirubin

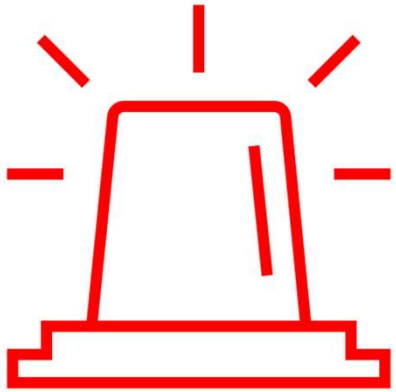


Acute Hemolytic XR

- Lab testing (cont.)
  - Disseminated intravascular coagulation (DIC)
    - Test for if the patient has obvious signs of intravascular hemolysis (pink serum or urine, hypotension), oozing from intravenous sites, or increased bleeding
      - Prothrombin time (PT) → prolonged
      - Activated partial thromboplastin time (aPTT) → prolonged
      - Fibrinogen → decreased
      - D-dimer → significantly increased
      - Platelet count → decreased
      - Peripheral smear → schistocytes
  - If signs of intravascular hemolysis → electrolyte testing and cardiac monitoring (lysed RBCs release potassium → hyperkalemia)
  - Serial hemoglobins

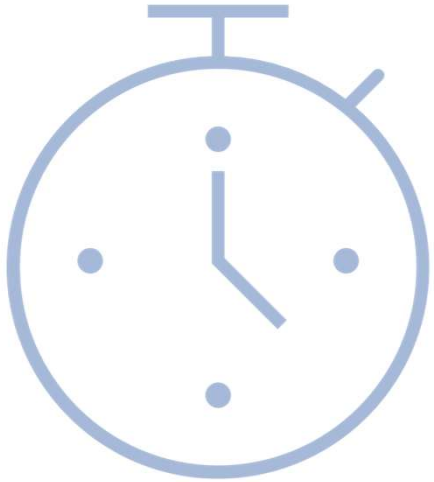
Acute Hemolytic XR

- Management
  - Medical emergency
  - Stop the transfusion
  - Immediate vigorous hydration and hemodynamic support
    - IV saline → to reduce the risks of hypotension and acute oliguric kidney failure
    - 100 to 200 mL/hour support a urine output above 1 mL/kg/hour
    - Once hemolysis resolves and the patient is clinically stable, no long-term interventions are needed
  - Notify the transfusion service
  - In severe cases, consider RBC/plasma exchange, IVIG, or complement inhibitors



Delayed Hemolytic XR

- Hemolytic TR that occurs more than 24 hours following transfusion
- Usually presents one to two weeks after transfusion of RBCs, although can be from 24 hours to 28 days
- Usually because antibody titers are too low for initial detection
  - Titers increases due to the antigenic stimulation, “anamnestic response”
- Previous transfusion, pregnancy
  - Less commonly due to hematopoietic stem cell or organ transplant, sharing of IV needle
- Typically, due to Rh or Kidd antibodies

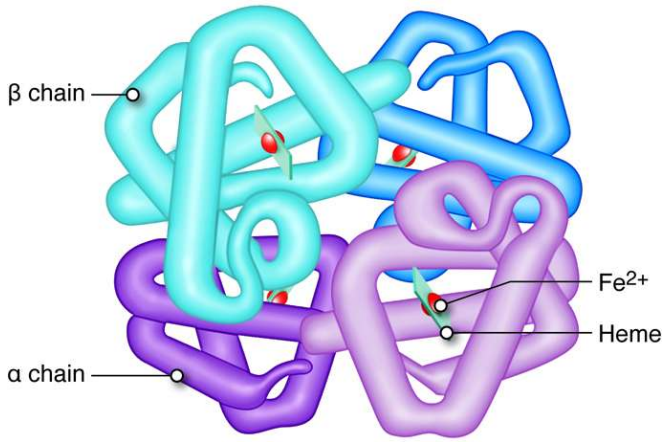


Delayed Hemolytic XR

- Case definition → definitive
  - Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion
    - AND EITHER
  - Positive elution test with alloantibody present on the transfused red blood cells, OR
  - Newly-identified red blood cell alloantibody in recipient serum
    - AND EITHER
  - Inadequate rise of post-transfusion hemoglobin level or rapid fall in hemoglobin back to pre-transfusion levels
    - OR
  - Otherwise unexplained appearance of spherocytes

Delayed Hemolytic XR

- Management
  - Monitor hemoglobin until it is clear that hemolysis has ended
    - Frequency depends on the severity of hemolysis
  - Unless brisk hemolysis, no intervention required, otherwise hydrate
  - Avoid future transfusions containing the implicated RBC antigen



Delayed Serologic XR

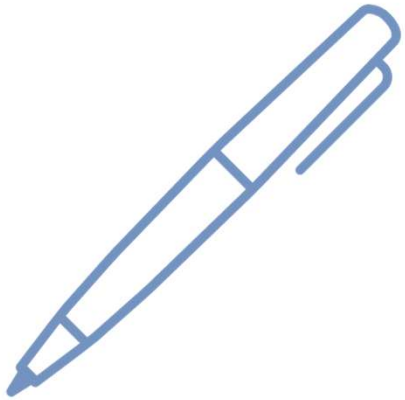
- Lab finding characterized by the development of new RBC alloantibodies following transfusion without clinical or laboratory evidence of hemolysis
- Occur when a patient with prior alloimmunization (from pregnancy or previous transfusion) has antibody titers that have fallen below detectable levels
- Antibodies most commonly responsible → Rh, Kell, Duffy, Kidd, MNS, and Diego
- Only about 0.5% develop symptoms

Delayed Serologic XR

- Case definition → definitive
  - Absence of clinical signs of hemolysis
    - AND
  - Demonstration of new, clinically-significant antibodies against red blood cells
    - BY EITHER
  - Positive direct antiglobulin test (DAT), OR
  - Positive antibody screen with newly identified RBC alloantibody

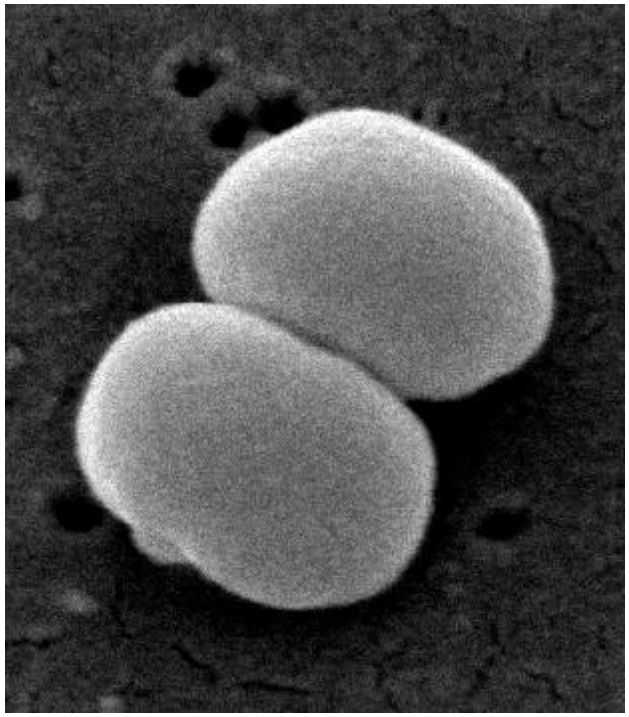
Delayed Serologic XR

- Management
  - Document the alloantibody, and inform the patient and caregivers of the importance of avoiding the antigen in future transfusions
  - Avoid future transfusions containing the implicated RBC antigen
  - Repeat antibody screening 1 to 3 months post-transfusion
  - For patients already heavily alloimmunized requiring long-term support…
    - Prophylactic rituximab (1000 mg IV, one or two doses)
    - Methylprednisolone has been used with some success



Transfusion-Transmitted Infection (TTI)

- Pathogen from a transfused blood component causes symptomatic disease in the transfusion recipient
- Most likely from platelets → usually stored at room temperature



TTI

- Risk
  - Bacteria → 1 in 60,000 transfusion
    - Gram-positive organisms are more common than gram-negative organisms
    - Usually a skin contaminant from when the product is collected during donation
  - Virus → substantially lower, e.g. approximately 1 in 2 million for HIV and HCV

TTI

- Case definition → definite
  - Laboratory evidence of a pathogen in the transfusion recipient

TTI

- Imputability → definite
  - ONE or more of the following:
    - Evidence of the pathogen in the transfused component
    - Evidence of the pathogen in the donor at the time of donation
    - Evidence of the pathogen in an additional component from the same donation
    - Evidence of the pathogen in an additional recipient of a component from the same donation
      - AND
    - No other potential exposures to the pathogen could be identified in the recipient
      - AND EITHER
    - Evidence that the recipient was not infected with the pathogen prior to transfusion
      - OR
    - Evidence that the identified pathogen strains are related by molecular or extended phenotypic comparison testing with statistical confidence ($p < 0.05$)

TTI

- Management
  - Stop the transfusion immediately
  - Maintain a patent IV line
  - Provide supportive/resuscitative care (hemodynamic, respiratory) as needed
  - Notify the blood bank
  - Save unused product and bag and return to the blood bank for testing
  - If TTI suspected
    - Collect two sets of blood cultures by venipuncture.

TTI

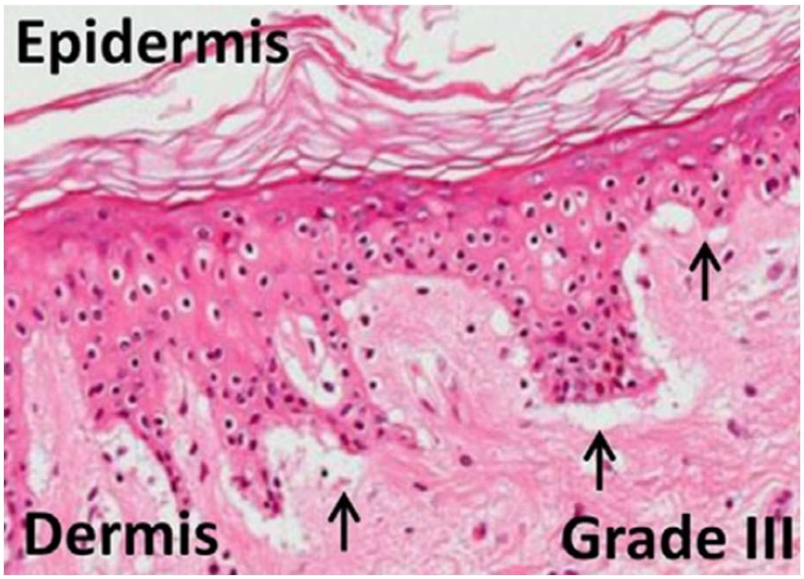
- Management (cont.)
  - Begin empiric antibiotic therapy after cultures are obtained, guided by the gram stain of the implicated product, if applicable
  - Once culture results available:
    - Specific organism is identified → antibiotics narrowed to cover that organism
    - Patient experiences clinical deterioration → antibiotics can be expanded
    - Blood product cultures negative and alternative explanation for the patient's clinical findings → stop antibiotics

TTI

- Asymptomatic patient with notification of a positive culture from the blood collection center
  - Decision to start antibiotics is individualized
    - Positive culture may represent a contaminant introduced during sampling of the unit
    - Patient may not warrant changes in management
  - Patient at high risk for infection, e.g. neutropenia
    - Increased surveillance and blood cultures
    - Start antibiotics pending blood culture results
  - Patient has an unexplained increase in WBC or CRP, or they will be away from direct medical care
    - May be reasonable to obtain blood cultures and start empiric antibiotics pending the blood culture results

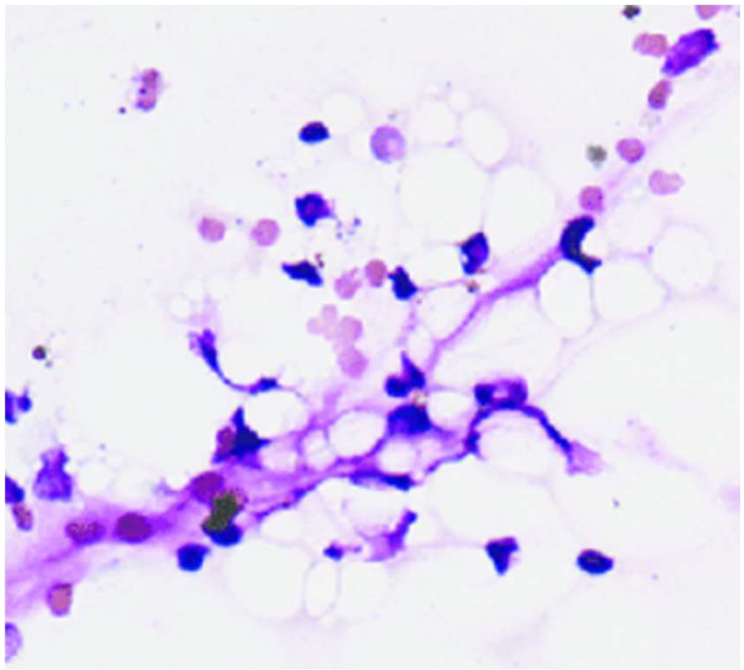
Transfusion-associated graft-versus-host disease (TA-GVHD)

- Rare and usually fatal complication of blood transfusion
- Lymphocytes from the transfused blood component attack the recipient's tissues, especially the skin, bone marrow, and gastrointestinal tract
- Recognition is often delayed because nonspecific symptoms are attributed to the patient's underlying diagnosis or another condition such as infection



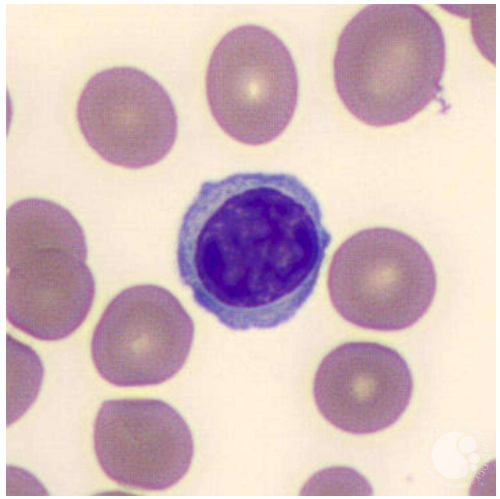
TA-GVHD

- Leads to bone marrow aplasia and profound pancytopenia → cause of death
- No highly effective treatments, so prevention is essential → irradiate blood products depending on the patient's condition



TA-GVHD

- Pathogenesis
  - When transfused lymphocytes are viable and one of the following is present
    - Recipient is immunosuppressed
    - Partial HLA matching between the transfused product and the recipient
  - Viable T lymphocytes from the transfused blood component are able to engraft, proliferate, and attack HLA-expressing tissues in the host



TA-GVHD

- Risk factors
  - Immunocompromised
  - Hematologic malignancy
  - Immunosuppressive drugs
  - Hematopoietic stem cell transplant
  - Fetus, neonate
  - Partial HLA match → directed donation from a relative

TA-GVHD

- All blood products have been implicated
- Extremely rare
  - True incidence is unknown and is expected to vary by population and preventive strategies used

TA-GVHD

- Case definition → definitive
  - A clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by:
    - Characteristic rash: erythematous, maculopapular eruption centrally that spreads to extremities and may, in severe cases, progress to generalized erythroderma and hemorrhagic bullous formation.
    - Diarrhea
    - Fever
    - Hepatomegaly
    - Liver dysfunction (i.e., elevated ALT, AST, Alkaline phosphatase, and bilirubin)
    - Marrow aplasia
    - Pancytopenia
      - AND
    - Characteristic histological appearance of skin or liver biopsy

TA-GVHD

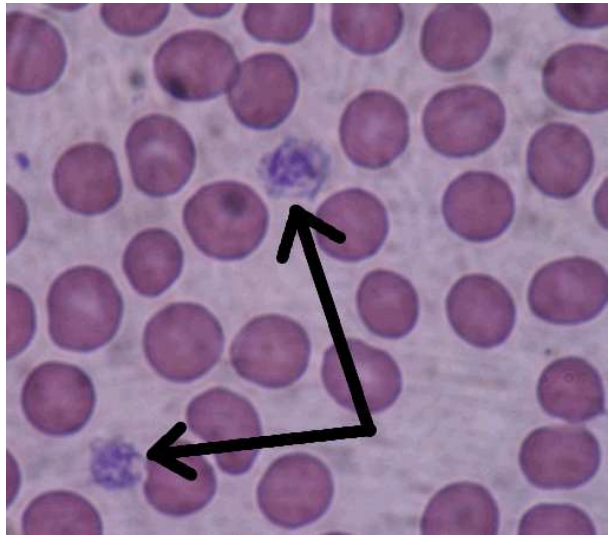
- Prevention
  - Irradiate products for high-risk individuals
    - Intrauterine transfusion
    - Neonatal exchange transfusion
    - Congenital cell-mediated immunodeficiencies
    - Hodgkin's lymphoma (all transfusions during patient's lifetime)
    - Hematopoietic stem cell transplant recipients (autologous or allogenic)
    - Donors of allogeneic hematopoietic stem cells (only applies to the week prior to and during stem cell harvest)
    - CAR-T therapy recipients (applies 7 days prior to collection and 3 months post-infusion
    - Purine analog therapy for any diagnosis
    - ATG or alemtuzumab therapy for hematologic disease (not other diagnoses)
    - Recipients of donations from biologic relatives
    - Recipients of donations selected on the basis of HLA matching

TA-GVHD

- Treatment
  - None effective except hematopoietic stem cell transplant (HSCT)
    - Rarely a viable option → usually insufficient time to identify an appropriate donor, test them for suitability to donate, and obtain sufficient hematopoietic stem cells for transplant
  - In some cases, immunosuppressive therapy has been effective in attenuating the course of the disease
  - Early recognition allows more time to institute supportive or immunosuppressive therapies, as well as to identify a potential hematopoietic stem cell donor
  - As soon as diagnosis is confirmed or strongly suspected, consult a provider with experience in managing patients undergoing HSCT with GVHD

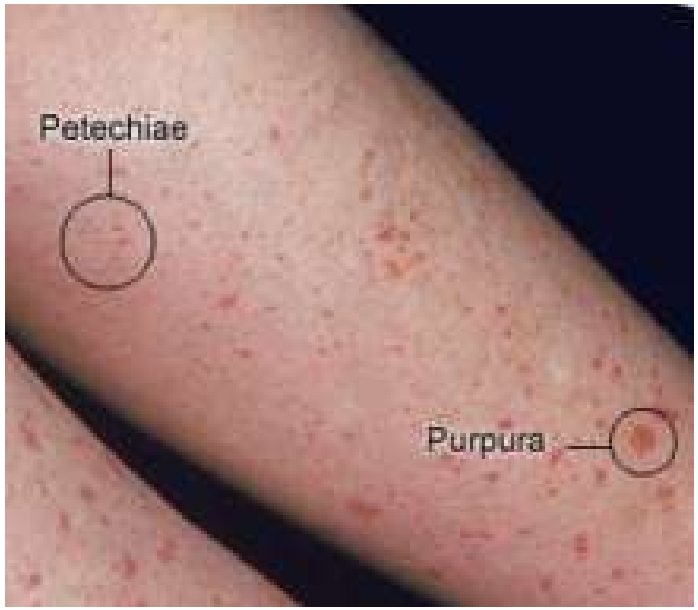
Post-transfusion purpura (PTP)

- About 1 in 50,000 to 100,000 transfusions
- Primarily in individuals sensitized to platelet antigens by exposure during previous pregnancy or transfusion
  - 26 to 1 female-to-male
- Any blood product
- Most common an antibody against human platelet antigen 1a (HPA-1a)



PTP

- Presentation
  - Severe thrombocytopenia → with platelet counts ≤ 20,000/microL
  - Purpura
  - Petechiae
  - Clinically significant bleeding
  - 5 to 12 days following transfusion
  - Lasts for days to weeks



PTP

- Case definition → definitive
  - Alloantibodies in the patient directed against HPA or other platelet specific antigen detected at or after development of thrombocytopenia
    - AND
  - Thrombocytopenia (i.e., decrease in platelets to less than 20% of pre-transfusion count)

PTP

- Treatment
  - High dose IVIG (400 to 500 mg/kg per day)
    - Usually for five days
    - 1 g/kg per day for two days can be given for severe thrombocytopenia
  - Takes about four days for the platelet count to exceed 100,000/microL

PTP

- Treatment (cont.)
  - Transfusion of antigen-negative platelets is generally not effective during the acute episode
    - Most platelets (even antigen-negative platelets) are destroyed
  - For patients who require a transfusion in the acute setting, avoidance of antigen-positive components is prudent

PTP

- Prevention
  - Subsequent transfusion should be blood products from an antigen-negative donor, or
  - Washed RBCs → removes antigen-positive platelets

Other

- If the recipient experienced an adverse reaction that is not defined in the Hemovigilance Module surveillance protocol
  - Transfusion-associated acute gut injury (TRAGI)
  - Transfusion-associated immunomodulation (TRIM)
  - Iron overload
  - Microchimerism
  - Hyperkalemia
  - Thrombosis

Unknown

- If the patient experienced transfusion-related symptoms, but the medical event that caused those symptoms could not be classified

Questions?

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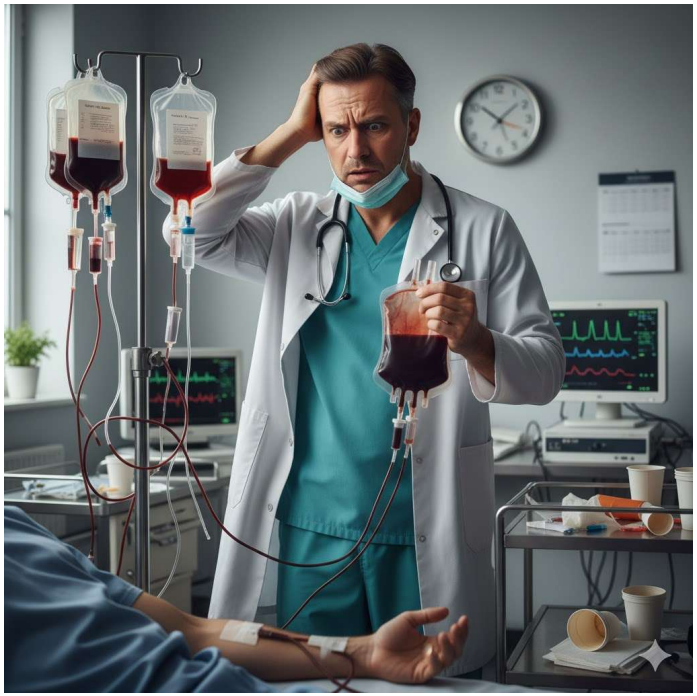
Outreach



- Physician available 24/7
  - Practitioners with transfusion-related questions/issues
  - Blood bank-related questions/issues
  - (515) 309-4840
- Education on transfusion-related topics
  - Presentations to medical personnel
  - Contact: alex.smith@lifeservebloodcenter.org
- Quarterly webinars
  - *https://www.lifeservebloodcenter.org/for-hospitals/resource-guide/education*
  - To request to be on the notification: shelly.schnell-petersen@lifeservebloodcenter.org

Thank you!

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