Complications of Blood Transfusion
Adverse Effects of Blood Transfusion

- ANY unfavorable consequence is considered an adverse effect of blood transfusion. It is also referred to as a Transfusion Reaction.

- The risks of transfusion must be weighed against the expected therapeutic benefits.
Complications of Transfusion

- Transfusion reactions occur in up to 10% of patients.
- Most common adverse side effects are usually mild and non-life-threatening.
Non-infectious Complications of Transfusions

- Acute (< 24°)
  - Immunologic
  - Non-immunologic

- Delayed (> 24°)
  - Immunologic
  - Non-immunologic
Acute (< 24°) Immunologic

- Hemolytic
- Fever/chills, non-hemolytic
- Urticarial/Allergic
- Anaphylactic
Acute (< 24°) Non-Immunologic

- Hypotension associated with ACE inhibition
- Transfusion-related acute lung injury (TRALI)
- Circulatory overload
- Nonimmune hemolysis
- Bacterial/Sepsis
**Estimated Frequencies of Some Adverse Effects of Transfusion**

| TYPE of Reaction             | Reported Frequency                                                                 |
|------------------------------|-----------------------------------------------------------------------------------|
| TACO                         | 1 : 68 to 1 : 356 (ICU patients) [Mortality 1 to 3%]                               |
| TRALI                        | 1 : 1200 to 1 : 190,000 [Leading reported cause of transfusion-related mortality] |
| WBC alloimmunization         | 1 : 20 to 1 : 100                                                                 |
| FNHTR’s                      | 1 : 100 – 200                                                                     |
| Cutaneous allergic           | 1 : 100 – 300                                                                     |
| Delayed serologic           | 1 : 1500                                                                          |
| Delayed hemolytic            | 1 : 4000                                                                          |
| Anaphylactoid               | 1 : 20,000                                                                        |
| Acute hemolysis             | 1 : 6,000 – 33,000                                                               |
| Anaphylactic                | 1 : 18000 to 1 : 170,000                                                        |
| Hypotensive TR’s            | 1 : 18,500                                                                        |
Acute (< 24°)
Immunologic

Hemolytic
Fever/chills, non-hemolytic
Urticarial/Allergic
Anaphylactic
Hemolytic

- Most severe hemolytic rxns. occur when transfused RBCs interact w/ preformed aby
- Transfused aby rxns. w/ recipient’s RBCs rarely cause sxs.
  - May cause accelerated RBC destruction
- Can occur after infusion of as little as 10-15 mL ABO-incompatible blood
- Etiology
  - 1:6,000 to 1:33,000
  - Clerical and other human error most common causes of ABO-incompatible transfusion
  - transfusion related deaths -23% (12%-15%)
  - Mortality estimated to be 1:1,00,000 -1:600,000 transfusion
Hemolytic

- Highly variable in acuity and severity
  - Severe
    - Fevers and/or chills
    - Hypotension
    - Dyspnea
    - Tachycardia
    - Pain
    - DIC
    - ARF
    - Shock
Hemolytic

Pathophysiology

- Intravascular hemolysis, opsonization, generation of anaphylotoxins
- Complement activation → classical pathway
  - IgM and IgG
  - C1q binds to Ig
  - C3 activation → cleavage of C3 leads to C3a being released into plasma and C3b deposition onto RBC membrane
    - C3a → proinflammatory effects
    - C3b → erythrophagocytosis
  - C5 cleaved → C5a into plasma
    - C5a → proinflammatory (100-fold more potent than C3a)
  - Assembly of remaining components of the MAC then occurs on RBC surface
  - Lysis of RBC

- Cytokines activation
  - TNF, IL-1, IL-6, IL-8

- Coagulation activation
  - Bradykinin
Hemolytic

- Laboratory findings
  - Hemoglobinemia
  - Hemoglobinuria
  - ↑ LDH
  - Hyperbilirubinemia
  - ↓ Haptoglobin
  - ↑ BUN, creatinine in ARF
  - DAT +
Hemolytic

- Differential diagnosis
  - AIHA
  - Nonimmune hemolysis
  - Microangiopathic hemolytic anemia
  - Drug-induced
  - Infections
  - Any causes of hemolysis
Hemolytic

Treatment/Prevention

- Stop transfusion
- Supportive care to maintain renal function
  - Goal of urine O/P 100 mL/hr. in adults for at least 18-24 hours
- Low dose dopamine
- Treatment of DIC
  - ? Heparin – direct anticomplement effect
- Prevention of clerical/human errors
Acute (< 24°)
Immunologic

Fever/chills, non-hemolytic
Urticarial/Allergic
Anaphylactic
Fevers/chills, non-hemolytic (FNHTR)

- Defined as a rise in temperature of 1°C or greater.
- Incidence
  - 43-75% of all transfusion rxn.
  - PRBCs 0.5-6%
  - Plts 1-38%
- Signs/Symptoms
  - Chills/rigor
  - RR-Blood pressure
  - Vomitting
Fevers/chills, non-hemolytic (FNHTR)

- Etiology
  - Reaction…
    - Between recipient WBC antibodies (HLA, WBC antigens) against transfused WBC in product
    - Cytokines that accumulates in blood bag during storage

- Differential Diagnosis:
  - Other causes of fever ruled out
    - Hemolytic
    - Bacterial/Septic

- Treatment/Prevention
  - Discontinue transfusion?
  - Acetaminophen/meperidine
  - Leukoreduced blood component
Acute (< 24°)
Immunologic

Hemolytic
Fever/chills, non-hemolytic

Urticarial/Allergic
Anaphylactic
Uritcarial/Allergic

- Continuum
  - Mild – urticarial
  - “Anaphylactoid”
  - Severe – anaphylactic

- Incidence
  - 1-3% of all transfusion rxn.

- Signs/Symptoms
  - Uriticarial/hives – upper trunk and neck
  - Pulmonary signs (10%) – hoarseness, stridor, “lump in throat”, bronchoconstriction
    - No cutaneous involvement
  - GI – N/V, abd. pain, diarrhea
  - Circulatory – tachycardia, hypotension
Uritcarial/Allergic

**Etiology**
- Circulating aby against soluable material in the blood
  - Proteins in donor plasma
- Binds to preformed IgE aby on mast cells
  - Release of histamine
- Vasoactive substances
  - C3a, C5a, leukotrienes

**Differential Diagnosis:**
- Hemolytic
- Bacterial
- TRALI

**Treatment/Prevention**
- Discontinue transfusion
- Antihistamine/steroids
- Washing of blood products, pretreatment, leukoreduction?
Acute (< 24°)
Immunologic

Hemolytic
Fever/chills, non-hemolytic
Urticarial/Allergic

**Anaphylactic**
Anaphylactic

- Rare

- Incidence
  - 1:18,000 to 170,000
  - Plt 1:1598-9630
  - FFP 1:28,831
  - RBCs 1:23,148-57,869

- Signs/Symptoms
  - In addition to urticarial/allergic...
    - Cardiovascular instability
      - Cardiac arrhythmia
      - Shock
      - Cardiac arrest
    - More pronounced respiratory involvement
Anaphylactic

**Etiology**
- IgA aby (IgE, IgG, IgM) in IgA deficiency
  - Serum IgA < 5 mg/dL
  - Estimated 1 in 342 blood donors
- C4 aby
- Aby against nonbiologic origin
- Haptoglobin deficiency (IgG or IgE anti-haptoglobin)
- ?

**Differential Diagnosis:**
- Hemolytic
- Bacterial
- TRALI
- Circulatory overload
Anaphylactic

- **Treatment/Prevention**
  - Discontinue transfusion
  - Supportive care
  - Epinephrine
  - Antihistamine/steroids
  - In IgA deficient pts. → IgA-deficient product, wash blood product
Acute (< 24°) Non-Immunologic

Hypotension associated with ACE inhibition
Transfusion-related acute lung injury (TRALI)
Circulatory overload
Nonimmune hemolysis
Bacterial/Sepsis
Hypotension associated with ACE inhibition

- Pt. on ACEI → receiving albumin during plasma exchange

Etiology
- Inhibition of bradykinin catabolism by ACEI
  - Bradykinin activation by activator (low level prekallikrein) in albumin
  - Bradykinin activation by prekallikrein in plasma protein

Differential diagnosis
- Rule out hemolysis

Treatment/Prevention
- Withdraw ACEI/supportive care
- Avoid albumin
- Avoid bedside leukofiltration
Acute (< 24°) Non-Immunologic

Hypotension associated with ACE inhibition

Transfusion-related acute lung injury (TRALI)

- Circulatory overload
- Nonimmune hemolysis
- Bacterial/Sepsis
Transfusion-related acute lung injury (TRALI)

What Is TRALI?
- Transfusion related noncardiogenic pulmonary edema
- Differential Diagnosis
  - Circulatory overload (TACO)
  - Allergic/Anaphylactic
  - Bacterial
  - Acute hemolytic reaction
- Clinical presentation ("classic", severe form)
  - Acute respiratory distress
  - Pulmonary edema
  - Hypoxemia
  - Hypotension
  - Transfusion usually within 6 hours (majority of cases during transfusion or within 2 hours of transfusion)
TRALI

- Clinical criteria
  - Insidious, acute onset of pulmonary insufficiency
  - Profound hypoxemia $\rightarrow$ PaO2/FiO2 $< 300$ mmHg
  - CXR $\rightarrow$ b/l fluffy infiltrates c/w pulmonary edema
  - Cardiac $\rightarrow$ PA wedge pressure $\leq 18$ mmHg
  - No clinical evidence of LA HTN
TRALI

Definition

- TRALI w/out clinical risk factors for ALI:
  - New ALI temporally related to transfusion
  - Worsening of pre-existing pulmonary insufficiency temporally related to transfusion

- TRALI in pts. w/ clinical risk factor for ALI:
  - New ALI temporally related to transfusion
  - New ALI thought to be mechanistically related to the transfusion
  - Worsening of pre-existing pulmonary insufficiency temporally related to transfusion
TRALI

• Syndrome of TRALI (Weber KE et al., *Transfusion Med Rev*, 2003)
  - Very common
    - Dyspnea, hypoxemia, pulmonary edema, hypotension, fever (1-2°C increase)
  - Common
    - Tachycardia, cyanosis
  - Uncommon
    - Hypertension
  - ?
    - Leukopenia, hypocomplements, monocytopenia
TRALI

- Implicated Blood Products
  - RBCs, FFP, apheresis platelets, platelet concentrates
  - Rare cases of IVIG, cryo-
  - No cases of albumin reported
TRALI

- Clinical Course
  - 100% TRALI patients require $O_2$ and 72% require ventilation support
  - 81% resolves within 4 days and 17% resolve within 7 days
    - Most pts. recover within 72 hours
  - No long term sequela
  - transfusion related deaths ;24% (14%-%25)

- Treatment
  - Respiratory support
  - No role for treatment w/ steroids or diuretics
TRALI

Why Is TRALI Important?

- Between 2001 – 2003, FDA report on causes of transfusion related deaths
  - TRALI 16.3%
  - ABO/Hemolytic transfusion reaction 14.3%
  - Bacterial contamination 14.1%
- UK SHOT Data 7 years experience (from 1996)
  - Total 155 cases
    - 32 Deaths
TRALI

- Pathogenesis
  - Two current working model hypothesis
  - Both models are directed against increase in pulmonary microvascular permeability

Leukocyte Antibody \[\rightarrow\] Pulmonary Microvascular Permeability \[\uparrow\] Bioactive Lipids

“Two-Hit” Model

\[\rightarrow\] Pulmonary Edema
TRALI

- UK and SHOT
  - What UK is doing
    - October 2003  Male donor ONLY for FFP
    - April 2004  Previously transfused donors excluded
  - Future Considerations
    - ? Male plasma only to suspend platelet pools
    - ? Female apheresis platelet donor for leukocyte antibody
    - ? Effects of decreased plasma (additive solution) in platelet concentrates/apheresis platelets
    - ? Mild TRALI. Does it exist?
Acute (< 24°) Non-Immunologic

- Hypotension associated with ACE inhibition
- Transfusion-related acute lung injury (TRALI)

**Circulatory overload**

- Nonimmune hemolysis
- Bacterial/Sepsis
Circulatory overload

- Acute pulmonary edema due to volume overload

Incidence

- One of the most common complications of transfusion
- Young children and elderly at risk
- Cardiac and pulmonary compromise
- Chronic anemia with expanded plasma volume
- Infusion of 25% albumin
  - Shifts large volume of extravascular fluid into the vascular space

Signs/Symptoms

- Dyspnea, cyanosis, orthopnea, HTN, CHF during or soon after transfusion
Circulatory overload

- Differential diagnosis:
  - TRALI
  - Allergic rxn.
  - Other causes of CHF

- Treatment/Prevention
  - Stop transfusion
  - Supportive care
  - Phlebotomy
  - Diuretic
  - Slow transfusion
    - Usually 4 hours, can be extended to 6 hours
    - Other strategies
# Comparing TRALI & TACO

| Similar Features          | TRALI                                    | TACO                                    |
|---------------------------|------------------------------------------|-----------------------------------------|
| Chest X-ray               | Diffuse bilateral infiltrates            | Diffuse bilateral infiltrates           |
| Respiratory Symptoms      | Acute dyspnea                            | Acute dyspnea                           |
| Auscultation              | Rales                                    | Rales                                   |

TRALI = transfusion-related acute lung injury; TACO = transfusion-associated circulatory overload
Comparing TRALI & TACO

| Disparate Features                   | TRALI                          | TACO                           |
|--------------------------------------|--------------------------------|--------------------------------|
| Temperature                          | Often elevated                 | Often unchanged                |
| Blood pressure                       | Hypotension                    | **Hypertension**               |
| Pulmonary artery occlusion pressure  | $\leq 18$ mm Hg                | $> 18$ mm Hg                   |
| Response to diuretic                 | Minimal                        | Significant                    |
| WBC count                            | May have transient leukopenia  | Unchanged                      |
| Pulmonary edema fluid                | Exudate                        | Transudate                     |
| Fluid balance                        | Positive, even, negative       | **Positive**                   |

- Patients with either may lack *typical* features
- Patients with TRALI may have TACO features
- TRALI & TACO may present concurrently
## TRALI vs. TACO

| TRALI | TACO |
|-------|------|
| **Signs & Symptoms** | **Signs & Symptoms** |
| Respiratory distress | Respiratory distress |
| Tachypnea | Tachypnea |
| Hypoxemia | Hypoxemia |
| Hypotension | Hypotension |
| Noncardiogenic pulmonary edema | Hypertension |
| Fever | Cardiogenic pulmonary edema |
| Onset within 6 hours of transfusion | Improves with diuretics |
| **Supporting Data** | **Supporting Data** |
| B/L pulmonary infiltrates on CXR | B/L pulmonary infiltrates on CXR |
| • Decreased WBC count | • Pretransfusion fluid overload |
| Associated with HLA and/or Neutrophil Antibodies | • Elevated BNP |
| | Increased heart size |
| | Vascular congestion |
| | Pulmonary wedge P > 18 mm Hg |
Acute (< 24°) Non-Immunologic

Hypotension associated with ACE inhibition
Transfusion-related acute lung injury (TRALI)
Circulatory overload

Nonimmune hemolysis
Bacterial/Sepsis
Nonimmune hemolysis

- Lysis of RBCs as a result of storage, handling, or transfusion condition

- Incidence
  - Rare

- Signs/Symptoms
  - Transient hemodynamic
  - Pulmonary impairment
  - Renal impairment
  - Hemoglobinemia and hemoglobinuria
  - Hyperkalemia (renal failure)
  - Fever
Nonimmune hemolysis

- **Differential diagnosis**
  - Hemolytic
  - Autoimmune
  - Bacterial/sepsis
  - PNH, drug-induced, oxidative stress, etc.
  - Diagnosis of exclusion

- **Treatment/Prevention**
  - Stop transfusion
  - Investigation of blood bag and tubing
  - Investigate for hemolytic transfusion rxn.
  - Check serum K
  - Supportive care
  - Maintain urine O/P (except for contraindication…i.e. renal failure)
Acute (< 24°) Non-Immunologic

Hypotension associated with ACE inhibition
Transfusion-related acute lung injury (TRALI)
Circulatory overload
Nonimmune hemolysis

Bacterial/Sepsis
Bacterial Contamination

* The source of the bacteria can be donor blood, donor skin flora, or contaminants introduced during collection, processing, and storage.

* Numerous gram-positive and gram-negative organisms can occur: Staphylococcus aureus, Klebsiella pneumoniae, Serratia marcescens, Pseudomonas and Staphylococcus epidermidis.
Bacterial Contamination

- Bacterial sepsis;
- Incidence : Pooled RDP : 1/700
  1 Unit of RBC: 1/31,000

- Rate of bacterial infection/contamination
- is higher with platelets is because they are stored at room temperature and the units are generally pooled between 6 and 10 donor units.
Bacterial Contamination

- Presentations:
- Fever
- Chills
- Tachycardia
- Hypotension
- Shock

The patient may also develop DIC and acute renal failure.
Bacterial Contamination

PREVENTION:

* Inspect all blood products for visual evidence of contamination

* The first 40 ml of blood collected is diverted in a pouch to reduce risk of transmitting organisms from skin
When a Reaction is Suspected...
Signs & Symptoms

- **GENERAL**
  - Fever
  - Chills
  - Muscle ache, pain
  - Back pain
  - Chest pain
  - Headache
  - Heat at the site of infusion or along vein

- **Nervous System**
  - Apprehension, impending sense of doom
  - Tingling, numbness

- **Respiratory**
  - Tachypnea
  - Apnea
  - Dyspnea
  - Cough
  - Wheezing
Signs & Symptoms

- Gastrointestinal
  - Nausea
  - Vomiting
  - Pain, abdominal cramping
  - Diarrhea (may be bloody)

- Renal
  - Changes in urine volume
  - Changes in urine color

- Cardiovascular
  - Heart rate
  - Blood Pressure
  - Circulatory
  - Bleeding

- Cutaneous
  - Rashes, Hives (urticaria)
  - Itching
Signs in an Unconscious Patient

- Weak Pulse
- Fever
- Hypotension
- Visible hemoglobinuria
- Increased operative bleeding
- Vasomotor instability
  - Tachycardia, brachycardia, hypotension
- Oliguria/anuria
Did the patient develop fever?

Yes
- Acute hemolytic
- FNHTR
- TRALI
- Bacterial contamination
  (Sepsis)

No
- Allergic
- Anaphylactic
- Hemolytic, FNHTR or TRALI

How high did the temperature rise?

<2°C

- Consider:
  - Acute hemolytic
  - FNHTR
  - TRALI
  - Bacterial contamination
  - Concomitant clinical factors

>2°C

Typically seen in
- Bacterial contamination
  (Sepsis)
When did the fever present?

Immediately/at start of transfusion:
- Bacterial contamination
- Acute hemolytic
- Concomitant clinical factors

During or at the end of the transfusion:
- FNHTR
- Bacterial contamination
- Acute hemolytic
- TRALI
- Concomitant clinical factors

Several hours after transfusion:
- FNHTR
- Bacterial contamination
- TRALI
- Concomitant clinical factors
