

- The term nonhemolytic febrile transfusion reaction defines an acute complication of blood transfusion characterized by fever with or without chills and rigors.
- These reactions are generally not life-threatening, but they cause discomfort; involve the use of medications; and employ resources of medical, nursing, and laboratory personnel.
- Most febrile reactions are due to immunologic reactions against one or more of the transfused cellular or plasma components, usually leukocytes. The use of leukocyte-depleted blood products minimizes the likelihood of nonhemolytic febrile transfusion reaction.

- an evolving and complex area of research and new knowledge.
- Leukocytes seem to be the main blood component responsible for the immunomodulatory effects of transfusion.
- Homologous transfusion has been shown to be an independent risk factor for postoperative infection..

transfusion-related immunomodulation

mechanisms of haemolysis before or during transfusion:

Immune destruction
Donor red cell serological incompatibility
Acute incompatible blood transfusion
Delayed haemolytic transfusion reaction
High-titre haemolysins in the donor plasma
Interdonor incompatibility
Destruction of donor red cells without detectable antibodies
Non-immune destruction
Transfusion of incorrectly stored or outdated blood
Inadvertently frozen blood
Overheated blood
Infected blood
Mechanical destruction, e.g. infused under pressure

Acute haemolytic transfusion reactions:

- Most severe acute hemolytic transfusion reactions usually have an identifiable and avoidable cause and result from an error at some point along the compatibility chain, most commonly incorrect patient identification.
- ABO incompatibility is the most common potentially fatal complication of blood transfusion, and meticulous attention to patient and sample identification is crucial.

Delayed haemolytic reactions:

- Most delayed hemolytic reactions are also immune in nature and usually cannot be prevented because the blood is serologically compatible at the time of transfusion. The clinician should always be on the lookout for the possibility of hemolytic episodes in critically ill patients because these are commonly due to reactions to blood transfusion or medications.

- apprehension,
- flushing,
- pain (e.g. infusion site, headache, chest, lumbosacral, and abdominal),
- nausea, vomiting,
- rigors,
- hypotension, and circulatory collapse.

Initial symptoms and signs

Hemostatic failure

- Coagulopathy due to disseminated intravascular coagulation may be a feature, resulting in generalized hemostatic failure, with hemorrhage and oozing from multiple sites.

- Because the responsible transfusion is likely to have been administered for hemorrhage, increasing severity of local bleeding may be the first clue to an incompatible transfusion, especially if the patient is under anesthesia.

- Renal failure may complicate a hemolytic transfusion reaction, and early recognition and prevention are crucial. If circulating volume and urinary output are rapidly restored, established renal failure is unlikely to develop.

Oliguria and renal impairment

Anaemia and jaundice

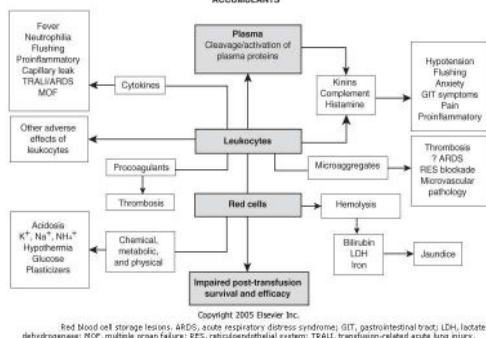
- A severe hemolytic transfusion reaction may be suspected from the development of jaundice or anemia.

- Blood is altered from the moment of its initial collection and subsequent storage.

- The storage lesions progressively increase until the time of expiry, and the extent of these changes is determined by the specific blood component, preservative medium, container, storage time, and storage conditions.

- Storage results in quantitative or qualitative deficiencies (or both) in blood components, which may reduce the efficacy of a transfusion.

ACCUMULANTS



problems from microaggregate infusion:

- Impaired pulmonary gas exchange (ARDS)
- Microcirculatory dysfunction
- Depression of RES function
- Depression of fibronectin levels
- Febrile reactions
- Activation of the haemostatic system
- Activation of the complement system
- Unnecessary antigenic stimulation
- Release of vasoactive substances

Storage lesions	Potential clinical consequences
Alterations in red blood cell structure and function	
ATP depletion	Echthymocyte formation, increased osmotic fragility, impaired RBC deformability with adverse effects on oxygen transport and delivery
Microvesiculation and loss of membrane lipid, lipid peroxidation and hemolysis, and irreversible damaged RBCs	Reduced RBC viability and cell death
Reduced 2,3-DPG	Hyperkalemia, LDH, increased serum iron, free radical generation (?), hyperkalemia
Increased hemoglobin affinity for oxygen and impaired unloading	
Reduced post-transfusion survival due to premature clearance post-transfusion	
Adverse effects on microcirculatory hemodynamics	
Hypothermia unless pretransfusion warming	
Additives	
Citrate	Hypocalcemia, acid-base imbalance, initial acidosis
Glucose	Hyperglycemia
Sodium	Hypernatremia
Cytokines: L-1, L-6, L-8, TNF	Fever, hypotension, flushing
Enzymes: Myeloperoxidase, elastase, arginase, secretory phospholipase A ₂	Transfusion-related immunomodulation, neutrophilia
Reactive proteins: Defense, anemoxin, soluble HLA, Fas ligand, soluble endothelial cell growth factor, and others	Proinflammatory, potential "priming" for ARDS, TRALI, and MODS
Histamine and kinin accumulation	Hypotension, anxiety, flushing, pain syndromes, proinflammatory
Microaggregates and procoagulants	Blockade of reticuloendothelial system
	Risk factor for development of ARDS, MODS, TRALI
	Activation of hemostasis > DIC (?), VTE (?), arterial thrombotic events (?)

red cell storage lesion

classification of transfusion reactions

Unifactorial Definite 1:1 Causation	Oligofactorial Probable 1:1 Causation + other factors	Multifactorial Possible Transfusion as risk factor
Compatibility HIV Hepatitis Endotoxaemia GVHD Technical error	Anaphylactoid reactions CMV Allergic reactions Fever TRALI	ARDS MODS TRIM Thromboses
Probability that transfusion is the cause		
Options for minimizing or preventing the adverse event		
Hazards of homologous blood transfusion, ARDS, acute respiratory distress syndrome, CMV, cytomegalovirus; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; MODS, multiorgan dysfunction syndrome; TRALI, transfusion-related acute lung injury; TRIM, transfusion-related immunomodulation.		

pathophysiology of transfusion reactions

- The pathophysiology of transfusion reactions can be divided broadly into three categories:
- 1. Reactions may occur due to IMMUNOLOGICAL DIFFERENCES between the donor and recipient
- 2. A wide range of INFECTIOUS AGENTS may be transmitted by homologous blood component therapy.
- 3. Alterations in blood products due to PRESERVATION & STORAGE

Impaired oxygen transport

- Microaggregates*
- Fluid overload
- Defective red cell function*
- Impaired haemoglobin function*
- Disseminated intravascular coagulation (DIC)*
- Acute respiratory distress syndrome (ARDS)*
- Multiorgan dysfunction syndrome (MODS)*

Haemostatic failure

- Dilution
- Depletion
- Decreased production
- Disseminated intravascular coagulation (DIC)*

Metabolic disturbances

- Electrolyte and metabolic disturbances*
- Hyperkalemia or delayed hypokalaemia*
- Sodium overload*
- Acid-base disturbances*
- Citrate toxicity*
- Hypothermia*

Vasoactive reactions

- Kinin activation*
- Damaged platelets and granulocytes*

Serological incompatibility

- Impaired reticuloendothelial function*

*Complications related to the method and time of storage

factors contributing to haemostatic failure in massive transfusion

- Pre-existing haemostatic defect
- Loss of coagulation factors, platelets and inhibitors
- Dilution of coagulation factors, platelets and inhibitors
- Impaired synthesis due to effects of shock on liver and bone marrow function
- Effects of trauma: disseminated intravascular coagulation and fibrinolysis
- Effects of storage lesion: depletion of coagulation factors and platelets, aggravation or precipitation of DIC
- Depletion of modulators of haemostasis (e.g. antithrombin III, fibronectin and protein C)
- Incompatible transfusion reaction: DIC
- Hypothermia
- Citrate toxicity?

allergic and anaphylactoid reactions

- Plasma reactions may be related to immunologic differences between the donor and the recipient; either the component is antigenic to the recipient or the plasma contains an antibody reacting with a recipient antigen.
- There may be physicochemical characteristics of the plasma component, such as temperature, additives, alterations due to preparative processes, and accumulation of metabolites or cellular release products on storage. Of particular importance in this respect are the complement and the kinin/kininogen systems. If these systems are activated, there may be generation of vasoactive substances and anaphylotoxins
- Clinical severity may range from minor urticarial reactions or flushing to fulminant cardiorespiratory collapse and death.

post-transfusion purpura

- a potentially life-threatening complication of transfusion in which platelet-specific alloantibodies develop at 5 to 10 days with the patient developing severe thrombocytopenia.
- Paradoxically, in contrast to other immunologically mediated transfusion reactions, the patient's own platelets are destroyed during the immunologic reaction.
- Early recognition of this rare complication, which typically occurs in women, is essential to minimize morbidity and mortality. Platelet transfusions are usually ineffective even if crossmatch compatible, and high-dose intravenous immunoglobulin (2g/kg given over 2 to 5 days) is the recommended treatment.

transfusion-associated graft-versus-host disease

- due to the infusion of immunocompetent lymphocytes precipitating an immunologic reaction against the host tissues.
- most commonly observed in immunocompromised patients, but also may be seen in recipients of directed blood donation from first-degree relatives and occasionally when donor and recipient are not related due to homozygosity for HLA haplotypes for which the recipient is heterozygous.
- Transfusion-associated graft-versus-host disease is generally a devastating and fatal condition, with onset of the syndrome 2 to 4 weeks after homologous transfusion with fever, liver function test abnormalities, profuse watery diarrhea, erythematous skin rash, and progressive marrow failure.

infectious complications

RISK OF TRANSFUSION-RELATED INFECTIONS		
Hazard	Minimization/prevention	Risk*
Bacterial contamination	Donor selection and collection technique	up to 1 in 80 000
HIV	Donor selection and viral testing	~1.4 × 10 ⁶
HBV	Donor selection and viral testing	~1.3 × 10 ⁶
HTLV I and II	Donor selection and viral testing	~1.1 × 10 ⁶