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Blood Transfusion Reactions

John Ayodele Olaniyi

Abstract

Blood transfusion reaction/adverse transfusion reactions could be fatal/severe or mild, immediate or delayed, immunological or nonimmunological, and infectious or noninfectious, and attention is paid particularly to the incidence, possible causes and pathophysiology, clinical features, and management of each type with the aim of improving awareness and raising consciousness towards improving blood safety and judicious use of blood so as to forestall these blood transfusion reactions as much as possible. This chapter serves as a synopsis to adverse blood reactions, which are very common but apparently more often under-recognized and/or under-reported particularly in developing countries. This should sharpen the consciousness of all health practitioners involved in blood transfusion services towards taking measures at preventing transfusion reactions right from donor selection up to the infusion of blood into the recipients.

Keywords: adverse blood reactions, blood safety, judicious use of blood, clinical features, management, immunological, immediate, infectious

1. Introduction

Blood transfusion remains a life-saving therapy and according to World Health Organization (WHO) guidelines, of 10 units per 1000 population, approximately 8 million units of blood are currently needed to meet the transfusion demand for a population of about 800 million [1]. While in the industrialized world, blood provision and blood safety are well established, in Africa, there is limited access to blood, and provision of unsafe blood renders blood safety a major public health concern. Blood transfusion may be needed in circumstances like obstetric hemorrhage, road traffic accidents, armed conflicts, sickle cell disease, anaemias especially in children, malnutrition, HIV, malaria, and parasitic infections. It is therefore important to always highlight the blood transfusion reactions, possible causes, expected symptoms and signs, preventive measures, and appropriate management. This will further encourage judicious use of blood and blood components.

2. What is blood transfusion reaction?

Blood transfusion reaction refers to undesirable, unintended, adverse response to the administration of blood, blood components, or derivatives that are well thought-out to be definitely probable or possibly related to this product. About 0.5–3% of all transfusions result in transfusion reaction.

Blood transfusion reactions can basically be categorized as infectious or noninfectious. The majority of blood transfusion reactions are, nonetheless,

noninfectious with outcomes ranging from nonsignificant consequences to death [2, 3]. However, the infectious effects are given more prominence than other adverse reactions.

For emphasis, when any unexpected or untoward symptom or sign occurs during or shortly after the transfusion of a blood component, a transfusion reaction must be considered as the precipitating event until confirmed otherwise [4].

3. Classification and incidence of adverse events

Broadly, BTR can be classified as infectious or noninfectious, immunological or nonimmunological, immediate or delayed, and mild or life threatening. The common, well known manifestations to all types of BTR include fever, chills, and urticaria [3, 5, 6] (**Table 1**).

3.1 The acute (life-threatening) BTRs

- Acute (immediate) haemolytic transfusion reaction

- Delayed haemolytic transfusion reaction

- Transfusion transmitted bacterial infection

- Anaphylaxis

- Transfusion-related acute lung injury (TRALI)

- Transfusion-associated circulatory overload (TACO)

3.1.1 Other acute noninfectious complications of blood transfusion

- Allergic reactions

- Anaphylaxis (IgA-deficient recipient)

- Lung damage from microaggregates (massive transfusion)

- Transfusion-associated circulatory overload ("TACO")

- Bacterial infection (mainly with platelet transfusion)

- Hypothermia (rapid infusion of refrigerated blood)

- Citrate toxicity/hypocalcemia (massive transfusion or apheresis)

- Graft-versus-host disease

- Air embolism

3.1.2 Classification of transfusion reactions based on immune or nonimmune

- Acute immunological (<24 hours)
  - Immediate (acute) haemolytic transfusion reaction
  - Febrile nonhemolytic.

- ○ Minor/major allergic.

- ○ Anaphylaxis.

- ○ TRALI.

- ○ Acute nonimmunological (<24 hours).

- ○ Bacterial contamination.

- ○ Transfusion-associated circulatory overload (TACO).

- • Delayed immunological (>24 hours).

  - ○ Delayed haemolytic transfusion reaction.

  - ○ Other delayed reactions.

  - ○ Minor/major allergic.

  - ○ Anaphylaxis.

- • Delayed nonimmunological (>24 hours).

  - ○ Transfusion transmissible infections (TTIs) (HIV/HBV/HCV).

  - ○ Transfusion-associated circulatory overload (TACO).

Tables 1, 3 and **5** refer to classification of BTRs.

Acute transfusion reactions	Delayed transfusion reactions
Acute haemolytic reaction (AHTR)	Delayed haemolytic reaction
Anaphylaxis	Transfusion transmitted infection
Bacterial contamination of blood component	Transfusion-associated graft-versus-host disease
Transfusion-associated acute long injury	Post-transfusion purpura
Transfusion-associated circulatory overload (TACO)	Iron overload
Allergic reaction	Immunosuppression
Febrile nonhemolytic transfusion reaction (FNHTR)	

Table 1.
Types of blood transfusion reactions.

Adverse events	Risk/unit
Mild allergic	1 in 100
FNH	1 in 300
TACO	1 in 700
TRALI	1 in 10,000
Bacteria contamination	1 in 10,000
Anaphylactic	1 in 40,000
Fatal haemolytic	1 in 1,000,000
HIV/HBV/HCV	1 in 1,000,000 to 8,000,000

Table 2.
Frequency of transfusion reactions.

3.2 Frequency of transfusion reactions

The risk per unit for each adverse event is as stated in **Table 2**.

4. Common signs and symptoms of blood transfusion

Although the signs and symptoms of BTR will be fully discussed under each type of blood transfusion reaction, it is important that these features be highlighted as it relates to each system.

i. Circulatory: circulatory changes include changes in blood pressure, tachycardia, arrhythmia, bleeding, blood in urine, and increase in bleeding tendencies.

ii. Pulmonary: pulmonary features include shortness of breath, dyspnea, wheezing, cough, and changes on chest X-ray.

iii. Immune: itching, rash/hives, flushing, fever, and chills/rigors.

iv. Others: Unexplained discomfort, back pain, chest pain, pain at the site of intravenous infusion and along the course of the vein, and anxiety.

4.1 Recognition at bedside

The complex background clinical condition of critically ill patients could mask the symptoms of a serious blood transfusion reaction; therefore, ventilated patients could have increased peak airway pressures, hyperthermia, and changes in urine output or color in the context of a blood transfusion, during a massive transfusion protocol. Therefore, monitoring core temperature, prompt use of measures to avoid hypothermia, using blood warmers, watch for hypocalcaemia, acidosis, and hyperkalemia go a long way in unmasking blood transfusion reactions.

5. Types of transfusion reactions

5.1 Minor transfusion reaction symptoms

A BTR is regarded as minor if:

• The hives or rash cover less than 25% of the body and there are no other symptoms.

• The fever (1°C rise over baseline and higher than 38°C) is associated with no other symptoms.

Quick steps to take when temperature increases by >1°C and >38°C (**Table 3**)

• Stop transfusion

• Clerical check

• Notify physician

• Notify blood bank

If clerical error is established or additional serious symptoms are identified, do not order for restart of blood transfusion. Instead

- Administer acetaminophen 325 mg

- Continue to monitor patient carefully and frequently

- Stop transfusion if symptoms worsen or additional symptoms develop

- If uneventful, complete transfusion reaction investigation form

- Send to blood bank with blood sample as per algorithm

Suspect

- Hemolytic transfusion reaction

- Bacterial contamination

Initiate transfusion reaction if the abovementioned points are excluded in investigation by

- Completing form 3.

- Collecting blood samples

- Sending blood bag to blood bank

- Continuing to monitor patient

- Reporting the condition to physician

The predominant symptom of a fever is most commonly seen in:

- Acute hemolytic transfusion reactions (AHTR)

- Febrile nonhemolytic transfusion reactions (FNHTR)

- Bacterial sepsis or contamination

5.2 Febrile nonhemolytic transfusion reaction (FNHTR)

The incidence of FNHTR is 1 in 300 for RBC concentrate transfusion and 1 in 20 for platelet concentrate transfusion.

Pathophysiological FNHTRs develop in patients that already have anti-leukocyte antibodies. Anti-leukocyte antibodies are raised in multiply transfused patients and multiparous women usually following RBC or platelet transfusions. In addition, donor-derived leukocytes present in platelets and RBC products liberate cytokines in the course of storage of blood and may also mediate NHTRs. Such cytokines include IL1, IL6, IL8, and TNF. Therefore, pre-storage leukoreduction may reduce the accumulation of these biologic mediators and the incidence of febrile, hypotensive, or hypoxic transfusion reactions.

Check for haemolysis

Perform visual examination of patient's plasma and urine (plasma and urine hemoglobin can be checked but this is not essential).

Blood film may show spherocytosis.

Bilirubin and lactate dehydrogenase (LDH) levels will be raised.

Check for incompatibility

Check the documentation and the patient's identity.

Repeat ABO group of patient pre-transfusion and post-transfusion and of the donor unit(s).

Screen the patient for red cell antibodies pre-transfusion and post-transfusion

Repeat crossmatch with pre-transfusion and post-transfusion samples.

Direct antiglobulin test (DAT) on pre- and post-transfusion samples.

Eluate from patient's red cells.

Check for disseminated intravascular coagulation

Perform blood count and film, coagulation screen, and fibrin degradation products (or D-dimers).

Check for renal dysfunction

Check blood urea, creatinine, and electrolytes.

Check for bacterial infection

Take blood cultures from the patient and donor unit including immediate Gram stain.

Immunological investigations

Check immunoglobulin A (IgA) levels and anti-IgA antibodies.

Table 3.
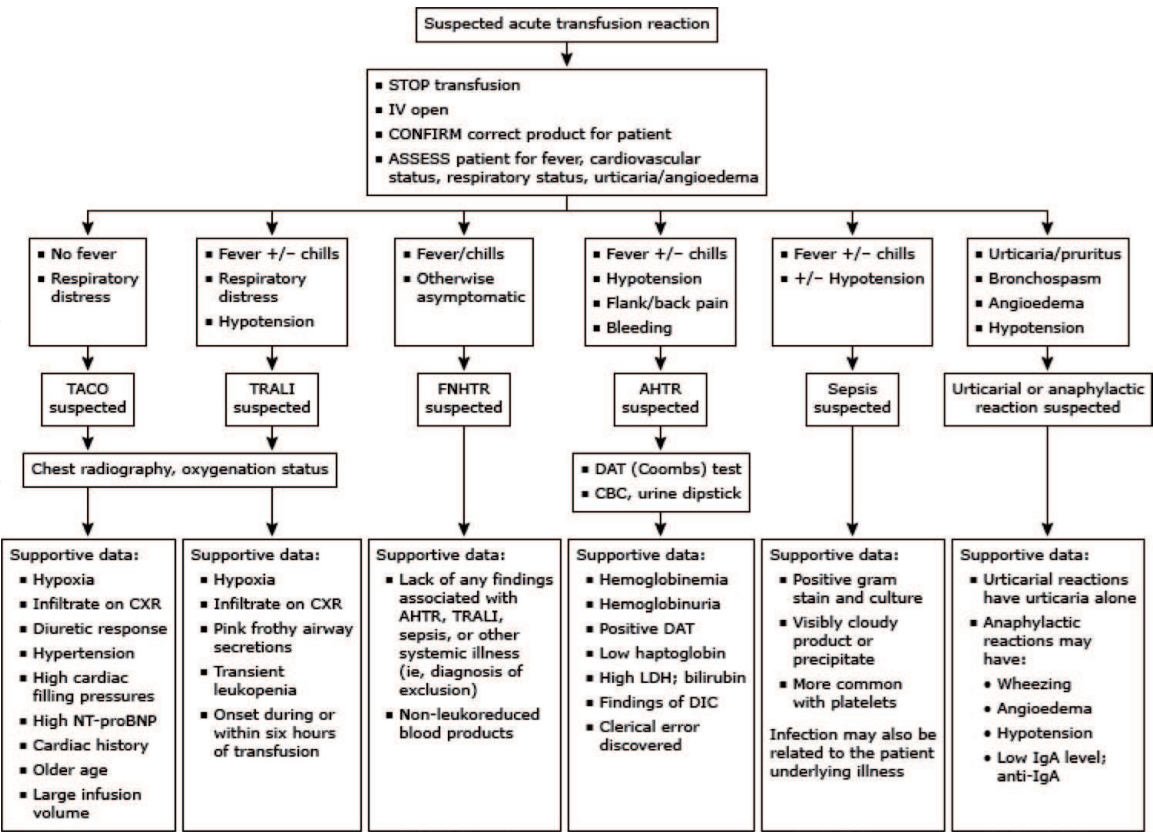*Investigations indicated in transfusion reactions.*

Clinical presentation: fever during transfusion or up to 4 hours after. The patient may also experience chills, rigors, nausea and vomiting, and hypotension without fever. FNHTRs typically manifest during or within 4 hours of transfusion with fever (defined as an increase in temperature of 1°C above the patient's baseline temperature, typically to 38°C) with or without chills and/or rigors. Such reactions may also manifest primarily with chills and/or rigors with minimal or absent febrile component particularly in patients receiving antipyretics. Symptoms are self-limited and respond to symptomatic treatment, which includes antipyretics for fever and chills and meperidine for rigors. Close differentials to FNHTRs include acute haemolytic transfusion reaction and septic transfusion reactions and patients' underlying medical condition. Therefore, it is important to do necessary investigations to rule out haemolysis. Leukoreduction has been associated with significant reduction in FNHTRs.

Management: blood transfusion should be stopped immediately and the ordering physician should be informed. Blood transfusion may be restarted cautiously as directed after the thorough investigation (**Table 3** and **Algorithm 1**).

5.3 Acute haemolytic transfusion reaction (AHTR)

The incidence of AHTR is 1 in 38,000. It is caused by transfusion of incompatible ABO blood group to a patient. It can be fatal with a mortality rate of about 10% and the risk of death is directly proportional to the amount of incompatible blood transfused.

Clinical presentation: fever and chills happen to be the most common feature. Anxiety, pain at the site of infusion, nausea/vomiting, back pain, dyspnea, flushing, wheezing and passage of red color urine, haemoglobinuria, hypotension, renal failure, disseminated intravascular coagulation (DIC), and shock may occur as late/terminal complications.

Algorithm 1.
Algorithm to follow in investigating acute transfusion reaction.

Pathophysiology: the ABO isohemagglutinins are compliment fixing and lead to intravascular destruction of transfused red cells which can manifest as hemoglobinemia and haemoglobinuria. Often, fever is the only initial sign. Activation of compliments leads to the release of cytokines like tumor necrosis factor, which is responsible for the fever and chills. The serologic hallmark of acute haemolytic reaction is a positive direct antiglobulin test (DAT), which demonstrates both IgG and compliment on the surface of recipient circulating red cells. Disseminated intravascular coagulation also occurs and bleeding may result.

Possible sources of error/causes include patient misidentification due to clerical error or failure to follow established hospital procedures. Therefore, definitive bedside patient identification, both at the time type and screening specimen, is being obtained, and the time the product is to be administered is very crucial. It has been advocated that the risk of mistransfusion can be greatly reduced by using barcode and radiofrequency chip technologies in order to ensure correct patient identification.

Also, AHTR can occur after platelet transfusions, typically involving a group A patient receiving group O platelets that contain high titer anti-A antibody.

Management: the treatment of AHTR is mainly supportive and it includes taking the following steps:

• STOP the transfusion!

• Check if any clerical errors in identifying the patient, blood group, and product label

• Notify the practitioner and blood bank, return product, and recollect sample from patient to confirm blood group

- Monitor patient closely

- Institute fluids and vaso-pressures for hypotension and urinary output.

5.4 Bacterial sepsis or contamination

The incidence of bacterial contamination for RBC is 1 in 50,000, 1 in 250,000 symptomatic septic reactions, and 1 in 500,000 with fatal bacterial sepsis. The incidence of bacterial contamination for platelet is 1 in 1000 with 1 in 10,000 symptomatic septic reactions and 1 in 60,000 fatal bacterial sepsis. About 10% of transfusion-related deaths are associated with bacterial sepsis.

Clinical presentation: the clinical features are similar to that of AHTRs and comprises of chills, rigors, high grade fever, tachycardia, hypotension, nausea, and vomiting. Disseminated intravascular coagulation (DIC) and shock may occur. Close examination of blood bag may reveal clots and change in color of blood in the bag compared to blood in the segmented tubing. There is no obvious focus of infection in the patient. The reaction typically develops 9–24 hours post transfusion and usually in neutropenic patients.
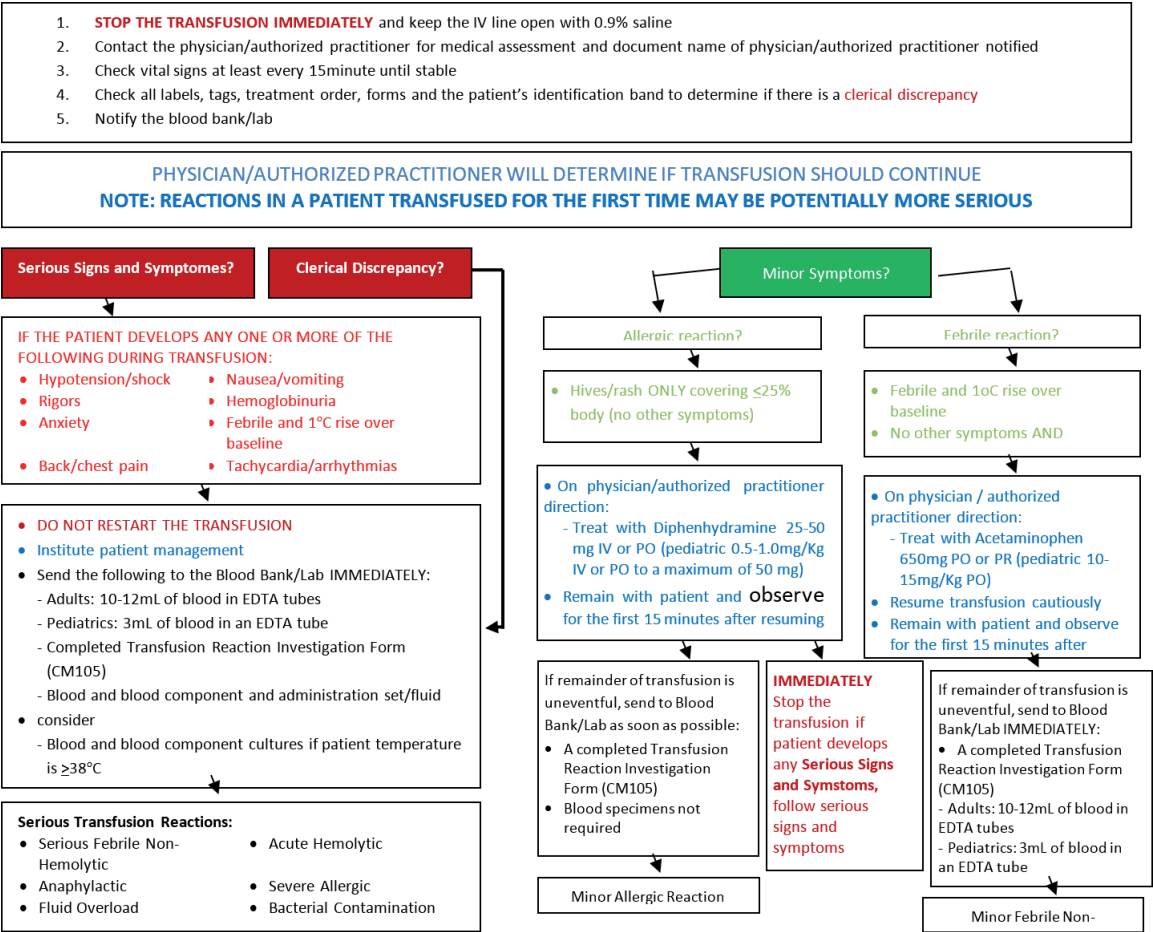
Management: such blood transfusion should be discontinued, if suspected and a doctor should be notified immediately who will notify and return the product to the blood bank after careful documentation of events. Necessary investigations should be carried out notably and blood culture samples should be collected. All necessary supportive interventions should be applied as dictated by the patient's clinical condition and the patient should be closely monitored. Also, abnormal bleeding or oozing in a patient during surgery that is equally having blood transfusion may raise suspicion of acute haemolytic transfusion reaction with DIC and appropriate management should be promptly applied (**Algorithm 2**).

5.5 Delayed haemolytic transfusion reaction (DHTRs)

In DHTRs, the patients develop an alloantibody to an RBC antigen following previous transfusion, pregnancy, or HSCT. Such red blood cell alloantibodies may decrease in titer although remaining clinically important, and hence, the patient has apparently negative antibody screening because the titer of the antibody has fallen below the detectable limit. In the event of a subsequent transfusion, the patient develops an anamnestic immune response to the mismatched antigen leading to delayed antibody-mediated destruction of transfused RBCs.

Clinical manifestation of AHTRs occurs 5–15 days post transfusion and it comprises haemoglobinuria, jaundice, and pallor as a result of the acute haemolytic process. In the context of a sickle cell disease patient (SCD) that often receives blood transfusion because of hyper-haemolytic crises, these features of haemolytic transfusion reaction are often accompanied by features of vaso-occlusive crisis (VOC), that is, pain, fever, and acute chest syndrome. There is usually worsened anemia and reticulocytopenia. In fact, DHTR is often misdiagnosed as VOC in SCD patient and the patient is unduly further transfused which culminates in multi-organ failure [5–9].

When features of AHTRs manifest, the link to the preceding transfusion is not always obvious. Direct antiglobulin test (DAT) is often positive for IgG, with or without compliment, depending on the antibody if carried out at this point. Also, an eluate may be performed to remove the IgG coating the circulating RBCs in order to identify it because a positive DAT may be unspecific. The antibody screen may also demonstrate the presence of a new antibody, although this may lag behind a positive DAT by a few days. The haemolysis in DHTRs is IgG mediated and thus extravascular; however, it is noteworthy that alloantibodies to Kidd blood group
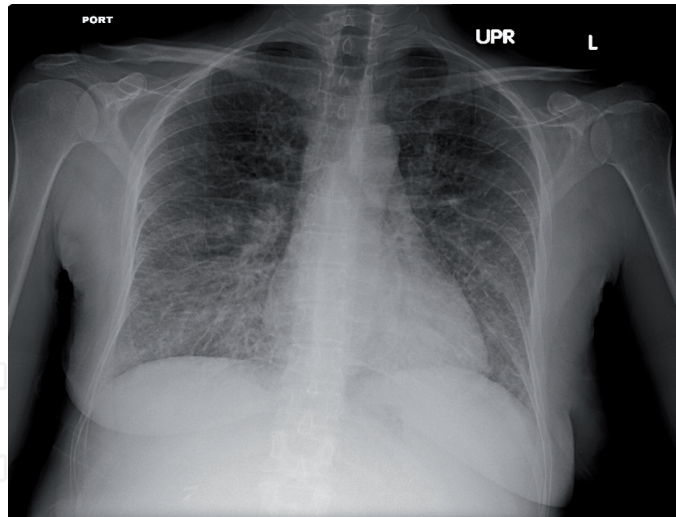
1. **STOP THE TRANSFUSION IMMEDIATELY** and keep the IV line open with 0.9% saline
2. Contact the physician/authorized practitioner for medical assessment and document name of physician/authorized practitioner notified
3. Check vital signs at least every 15minute until stable
4. Check all labels, tags, treatment order, forms and the patient's identification band to determine if there is a clerical discrepancy
5. Notify the blood bank/lab

PHYSICIAN/AUTHORIZED PRACTITIONER WILL DETERMINE IF TRANSFUSION SHOULD CONTINUE
NOTE: REACTIONS IN A PATIENT TRANSFUSED FOR THE FIRST TIME MAY BE POTENTIALLY MORE SERIOUS

Serious Signs and Symptoms? **Clerical Discrepancy?**   **Minor Symptoms?**

IF THE PATIENT DEVELOPS ANY ONE OR MORE OF THE FOLLOWING DURING TRANSFUSION:
- Hypotension/shock
- Rigors
- Anxiety
- Back/chest pain
- Nausea/vomiting
- Hemoglobinuria
- Febrile and 1°C rise over baseline
- Tachycardia/arrhythmias

- DO NOT RESTART THE TRANSFUSION
- Institute patient management
- Send the following to the Blood Bank/Lab IMMEDIATELY:
  - Adults: 10-12mL of blood in EDTA tubes
  - Pediatrics: 3mL of blood in an EDTA tube
  - Completed Transfusion Reaction Investigation Form (CM105)
  - Blood and blood component and administration set/fluid
- consider
  - Blood and blood component cultures if patient temperature is ≥38°C

Serious Transfusion Reactions:
- Serious Febrile Non-Hemolytic
- Anaphylactic
- Fluid Overload
- Acute Hemolytic
- Severe Allergic
- Bacterial Contamination

Allergic reaction?
- Hives/rash ONLY covering ≤25% body (no other symptoms)

- On physician/authorized practitioner direction:
  - Treat with Diphenhydramine 25-50 mg IV or PO (pediatric 0.5-1.0mg/Kg IV or PO to a maximum of 50 mg)
- Remain with patient and observe for the first 15 minutes after resuming

If remainder of transfusion is uneventful, send to Blood Bank/Lab as soon as possible:
- A completed Transfusion Reaction Investigation Form (CM105)
- Blood specimens not required

IMMEDIATELY Stop the transfusion if patient develops any **Serious Signs and Symstoms,** follow serious signs and symptoms

Minor Allergic Reaction

Febrile reaction?
- Febrile and 1oC rise over baseline
- No other symptoms AND

- On physician / authorized practitioner direction:
  - Treat with Acetaminophen 650mg PO or PR (pediatric 10-15mg/Kg PO)
- Resume transfusion cautiously
- Remain with patient and observe for the first 15 minutes after

If remainder of transfusion is uneventful, send to Blood Bank/Lab IMMEDIATELY:
- A completed Transfusion Reaction Investigation Form (CM105)
- Adults: 10-12mL of blood in EDTA tubes
- Pediatrics: 3mL of blood in an EDTA tube

Minor Febrile Non-

Algorithm 2.
Necessary steps in the management of blood transfusion reactions.

antigens may fix compliment and cause intravascular haemolysis with consequent haemoglobinuria, and occasional instances of severe complications like acute renal failure or disseminated intravascular coagulation have been reported. The antibodies most often implicated in DHTRs are directed against antigens in the Rh (34%), Kidd (30%), Duffy (14%), Kell (13%), and MNSs (4%) [8, 10]

5.5.1 Management of DHTRs

Ensure leukocyte-poor products as a preventive measure (refer **Algorithm 2**).

5.6 Transfusion-related acute lung injury (TRALI)

A consensus definition of TRALI is acute lung injury (ALL) occurring during a transfusion or within 6 hours of completing a transfusion with no other temporarily associated causes of acute lung injury (ALL). ALL is defined as (i) a syndrome of 10 acute onsets, (ii) hypoxemia ($PaO_2/FiO_2 < 300$ mm of Hg, O_2 saturation < 90% on room air or other clinical evidence), (iii) bilateral pulmonary infiltrates, and (iv) no evidence of circulatory overload [7, 11].

The development of TRALI, which is a potentially life-threatening reaction, is triggered by passive transfusion of donor anti-granulocyte antibodies (anti-HLA or anti HNA antibodies), cytokines, biologically active lipids, or other substances into the recipient. These cause acute lung injury with noncardiogenic pulmonary edema. The signs and symptoms comprise dyspnea, hypoxemia, hypotension, fever, and a chest X-ray showing bilateral lung infiltrates with pulmonary edema (**Figure 1**) [7, 11].

Figure 1.
CXR of a TRALI patient showing pulmonary infiltrates.

Management: aggressive pulmonary support including mechanical ventilation is frequently required. Approximately 80% of patients improve within 48–96 hours and all the patients require oxygen support with approximately 70% needing mechanical ventilation. Infrequently, antibodies in the recipient may react with donor granulocytes that were present in units of RBCs or platelets transfused. Strangely, in some cases of TRALI, neither recipient nor donor-derived antibodies can be identified. Other mechanisms have been advanced such as the priming of neutrophils by bioactive lipids that accumulate during blood storage (**Figure 2**) [7, 11].

The United States FDA in 2007 documented that TRALI represented 65% of all transfusion-related fatalities. The widespread implementation of TRALI risk reduction strategies adopted thereafter led to reduction to 37% of transfusion fatalities reported in the 5-year period from 2008 to 2012. TRALI remains the leading cause of death due to transfusion in the US.

The probable incidence rate of TRALI is about 1/5000 transfusions of plasma containing blood product, that is, RBCs, platelets, concentrate, platelet apheresis units, and plasma with a 5–10% fatality rate. TRALI may be difficult to differentiate from manifestations of patients underlying medical problems particularly those of cardiac origin, such as congestive heart failure and fluid overload brought on by transfusion.

Clinical management is supportive with the goal of reversing progressive hypoxemia. There is no universal method to prevent TRALI. Once blood from a particular patient is implicated in a case of TRALI, the donor is excluded from the donor pool. Preventing the first case of TRALI by those donors, however, requires the elimination of all blood donors whose plasma contain anti-HLA or anti-neutrophil antibodies. For plasma, this is achieved by excluding female donors from the plasma donor pool because multiparous females are most likely among a healthy donor population to have anti-HLA antibodies as a result of sensitization during pregnancy [7, 11]

When this approach was adopted in the UK in late 2003, where 60% of TRALI had been caused by plasma transfusions, no report of TRALI death due to plasma occurred after 2004 (6 deaths occurred in 2005, none from plasma). Major blood suppliers in the US now limit the use of female plasma or screen for HLA or HNA antibodies in multiparous donors. Even with these precautions in place, cases of TRALI in which HLA or any other granulocyte-specific antibodies do not appear to be responsible will not be eliminated.
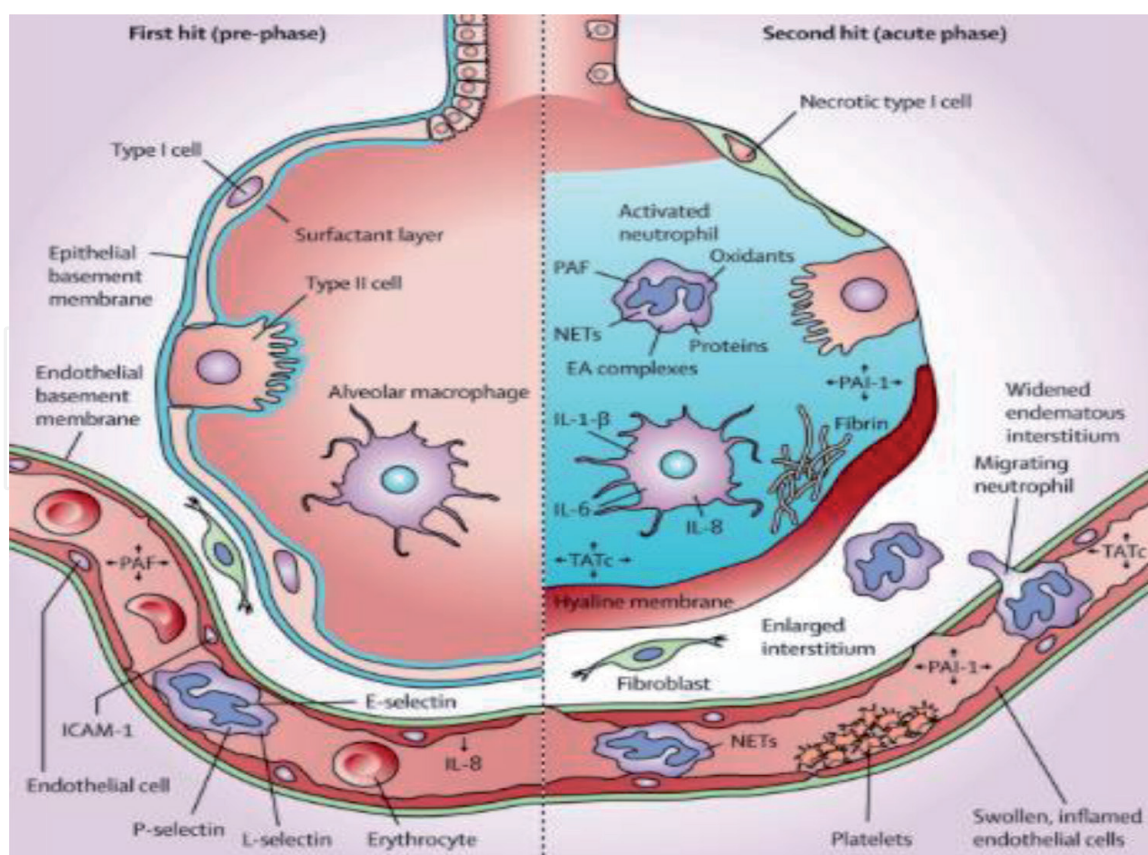
Figure 2.
Pathophysiologic mechanisms in TRALI. This figure illustrates inflammatory processes in the lung both during the "first hit" and during the "second hit" (acute phase) where the inflammatory processes are heightened than the "first hit". Mediators of inflammation in the infused blood products (FFP > platelets > RBCs) containing donor anti-granulocyte antibodies (anti-HLA and anti-HNA antibodies) along with cytokines and biologically active lipids activate inflammatory cascade through polymorph-nuclear cells (PMNs) with resultant capillary injury. As shown in the "second hit" section of the lung, the capillaries are congested, endothelial cells are swollen and inflamed, and there is increased platelet deposition and aggregation. The interstitial becomes more enlarged. There is increased adherence and migration of neutrophils of activated adhesion molecules (ICAM-1, P-Selectin, L-Selectin). Also, alveolar macrophages liberate inflammatory cytokines (IL-1b, IL-6, IL-8) and activated neutrophils elaborate PAF, NET compliments, and oxidant proteins. All these culminated in lung injury with noncardiogenic pulmonary edema causing hypoxemia, hypotension, pulmonary infiltrates, and fever.

Therefore, strict transfusion criteria for plasma-rich blood products, early recognition, and prompt clinical management are the keys to dealing with these potentially fatal transfusion reactions.

Reporting suspected cases of TRALI to the blood bank is also important in limiting potential risk to other patients by quarantine of any co-components from the same donation and evaluating the donor with possible exclusion from future donation if TRALI is confirmed [7, 11].

5.7 Transfusion-associated circulatory overload (TACO)

The incidence of TACO is 1/100 and the risk factors in TACO include patients with limited cardiopulmonary reserve, that is, the very young and the very old, high volume transfusion, background renal, or cardiac disease.

The onset is usually 1–2 hours post transfusion. TACO manifests as shortness of breath, cough, chest tightness, cyanosis, rales, orthopnea tachycardia, distended jugular veins, S3 gallop, and pulmonary edema, which are consistent with cardiac decompensation following volume overload [7, 12].

It is important that the vital signs of a patient under general anesthesia and on blood transfusion be continually monitored in order to be able to detect these features early and to be able to prevent TACO.

Managing

- Stop transfusion

- Position patient in upright position

- Supplementary oxygen

- Diuretics

- Cardiac and respiratory support as required

- Initiate transfusion reaction investigation

However, it is important to bear in mind the differences between TACO and TRALI (**Table 4**).

5.8 Allergic transfusion reactions

Allergic reactions following blood transfusions can be mild and frequently manifested by urticarial rash. Many urticarial reactions are donor-specific and thus do not occur with subsequent transfusion.

5.8.1 Management

If a recipient experiences multiple urticarial reactions, premedication with anti-histamines should be considered.

Washed products re-suspended in albumin or saline may be considered in severe cases. While removing plasma through washing mitigates allergic reactions, washing platelets impair platelet functions and lead to accelerated clearance after transfusion.

Antihistamines generally alleviate symptoms of allergic reactions but have not been proven to prevent them [7, 13].

5.8.2 Anaphylactic reaction

The incidence of anaphylactic reaction is put at 1 in 40,000 and the clinical presentation is characterized by widespread rash, shortness of breath cough, tachycardia, flushing, and anxiety.

	TRALI	TACO
Blood pressure	Low-normal	Normal-high
Body temperature	Normal-elevated	Normal
CXR	No vascular congestion	Vascular congestion, pleural effusion
BNP	Low (< 250 pg/ml)	High
PAOP	Low-normal	High
Ejection fraction	Normal function	Abnormal function
Response to diuretics	Inconsistent	Improved
Edema fluid	Transudate	Exudate

Table 4.
Differences between TRALI and TACO.

Severe IgA-deficient patients may make anti IgA antibody that can cause anaphylactic reaction, but this is a rare occurrence. Considering that approximately 1 in 1200 people is IgA deficient with anti-IgA antibodies and that passively transfused anti IgA antibodies do not cause allergic reactions, the pathophysiology of recurrent and severe allergic transfusion reactions in IgA deficiency is incompletely understood. Washed RBCs, washed platelets, and/or platelet and plasma products from IgA-deficient donors should be transfused only when a patient has severe IgA deficiency and a concern for anaphylactic reactions. Most IgA-deficient patients, even those with anti IgA, have no adverse reactions to transfusion. There are also reports of patients with deficiency of haptoglobin and various complement components such as C4a (Rogers antigen) or C4b (Chido antigen) developing anaphylactic reactions to platelets [7, 13].

Management: as illustrated in **Table 5** and **Algorithm 1**.

If hives/rash covers <25% of body stop transfusion; do the following: clerical check, notify physician, and notify blood bank.

If clerical error is identified or there are serious symptoms do not restart transfusion, the following should be ensured:

1. Administer diphenhydramine 25–50 mg IV/po

2. Continue to monitor patient carefully and frequently

3. Stop transfusion if symptoms worsen or additional symptoms develop

4. If uneventful, complete transfusion reaction investigation form

5. No need to send blood samples or blood bag

Temp increase by >1°C and >38°C	
1. Stop transfusion 2. Clerical check 3. Notify physician 4. Notify blood bank	
Clerical error or additional serious symptoms?	
No **Restart transfusion cautiously as ordered**	**Yes** **Do not restart transfusion**
1. Administer acetaminophen 325 mg 2. Continue to monitor patient carefully and frequently 3. Stop transfusion if symptoms worsen or additional symptoms develop 4. If uneventful, complete transfusion reaction investigation form 5. Send to blood bank with blood sample as per algorithm	1. Suspect hemolytic transfusion reaction or bacterial contamination 2. Initiate transfusion reaction investigation by completing form 3. Collect blood samples 4. Send blood bag to blood bank 5. Continue to monitor patient and report condition to physician

Table 5.
The protocol to follow in the case of emergence of fever during blood transfusion.

6. Infectious complications

6.1 Approximate risk per transfused unit of various infectious agents

The risk per transfused units for each infectious agent is as shown in **Table 6** [7].

Infectious agent	Approximate risk/transfused unit
Hepatitis B virus	1:750,000
Hepatitis C virus	1:1.1 million
HIV-1, HIV-2	1:2.7 million
Bacterial sepsis	1:75,000 (platelet transfusions)
Bacterial sepsis	1:250,000 to 1:10 million (red blood cell transfusions)

Table 6.
Infectious complications of transfusion.

6.2 Bacterial and parasitic transmissions by transfusion

In the United States, bacterial contamination of platelet products has been recognized as the most common cause of transfusion-associated morbidity and mortality owing to an infectious source. It exceeds hepatitis, HIV, and other viral sources put together. It was noted that the frequency of bacterial contamination is as high as 1 in 1000 to 1 in 2000 platelet units. It results in clinical sepsis after 1 in 4000 platelet transfusions before preventive measures were put in place. As an example, the introduction of bacterial screening has reduced the risk of septic transfusion reactions for apheresis platelets, and it has declined to approximately 1 in 75,000 with the risk of a fatal septic reaction declining to approximately 1 in 500,000 [7, 14, 15].

Efforts to detect the presence of bacteria in platelet units before dispensing to a patient include incubating an aliquot of the unit in a culture system and using a rapid strip immunoassay for bacterial antigens. Other less sensitive methods for detection using a surrogate marker for evidence of bacterial metabolism, such as a low pH, in an aliquot of the platelet suspension have been discontinued. While platelet products are typically contaminated by Gram-positive cocci, such as coagulase-negative Staphylococci, sepsis associated with transfusion of RBC units is most often due to Gram-negative organisms, particularly Yersinia enterocolitica.

Red blood cell contamination with Yersinia enterocolitica had resulted in bacteremia and septic shock which is often catastrophic. This Gram-negative organism can survive during refrigerated storage and lead to bacteremia or septic shock in the transfused recipient. Malarial transmission by transfusion is very common in Africa where malaria is known to be endemic but uncommon in Europe and America but cases are occasionally reported [7, 15].

6.3 Hepatitis

The estimated risk of post-transfusion hepatitis C is 1 per 1.1 million units transfused with current use of anti-hepatitis C virus antibody tests and nucleic acid testing.

Post transfusion hepatitis occasionally still develops despite the exclusive use of volunteer blood donors and screening of donor blood for hepatitis B and hepatitis C viruses. Transfusion-related hepatitis C virus infection is usually subclinical and anicteric in most cases but frequently becomes chronic and often results in clinically significant liver dysfunction [7, 15].

The risk of HBV transmission by transfusion decreased from 1:220,000 to approximately 1:750,000 after implementation of HBV DNA testing. Photochemical pathogen inactivation strategies appear both efficacious and relatively sparing in terms of qualitative platelet function, although decreases in quantitative platelet recovery have been observed in some studies [7, 15].

6.4 HIV and human T-cell lymphotropic viruses

The risk of acquiring HIV-1 or HIV-2 infection as a result of transfusion currently is estimated to be 1 in 1.5 million. Nucleic acid amplification testing for HIV has reduced the window of serologic conversion from 16 days to about 9 days. The use of heat-treated concentrates, solvent detergent-treated products, and recombinant factor concentrates has essentially eliminated HIV as a therapy-risk for hemophiliacs [7, 15].

6.5 Human T-cell lymphotropic virus 1 (HTLV-1)

This is a retrovirus associated with adult T-cell leukemia or lymphoma and tropical spastic paraparesis. Screening for HTLV-1 in blood donors is currently performed in the United States because asymptomatic blood donors can transmit this virus. Several cases of neuropathy had been reported in transfused recipients before the availability of testing.

HTLV-2, a related virus with antigenic cross-reactivity to HTLV-1, is endemic in certain Native American populations and also has been found in a high proportion of intravenous drug users. The risk of HTLV transmission by transfusion using current test methods is approximately 1 in 2.7 million [7, 15].

6.6 West Nile virus (WNV)

WNV became known to the US during the 2002 (WNV) epidemic in the United States wherein 23 individuals acquired WNV after blood transfusion. The characteristic clinical features manifested include fever, confusion, and encephalitis which developed within days to weeks of transfusion. As a result, blood centers implemented nucleic acid-based testing to screen all donations for WNV.

In a survey of 2.5 million donations in 2003, 601 donations (0.02%) were found to contain WNV. A subsequent follow-up study detected no cases of transfusion-transmitted WNV infection among recipients of tested blood; however, rare breakthrough transmissions have been reported [7, 15].

6.7 Parvovirus B19

Rare transmissions of parvovirus B19 by transfusion have been recognized. A recent study documented persistence of low levels of parvovirus B19 DNA in a high percentage of multi-transfused patients. The long-term clinical implications of this finding currently are unknown. Parvovirus (and other viruses without a lipid envelope such as hepatitis A virus) is not eliminated by solvent detergent treatment.

Acute parvovirus B19 infection can result in impaired erythropoiesis and can cause an aplastic crisis in patients with sickle cell disease and other hemolytic diseases. Infection with this virus can also result in significant fetal harm when a pregnant woman is infected during weeks 9–20 of pregnancy. There is no currently available blood donor screening assay for this virus [7, 15].

6.8 Cytomegalovirus (CMV)

CMV resides in leukocytes, and leukocytes inevitably contaminate RBC and platelet concentrate products. Hence, they are capable of transmitting CMV infection. Transfusion-transmitted CMV infection is an important issue in transfusion of cellular

blood products to neonates, particularly low-birth-weight infants born to seronegative mothers, HSCT recipients, and other highly immunosuppressed patients [7, 15].

The risk of acquiring CMV from transfusions is particularly high when pre-transplantation serologic testing reveals that neither the HPSC donor nor the recipient has been previously exposed to CMV. In addition, transplantation recipients are at increased risk for transplantation-associated CMV reactivation when either the donor or the recipient is seropositive for CMV before transplantation. The latter consideration often affects the choice of HPSC donors. For these reasons, some institutions use blood products obtained exclusively from CMV-seronegative donors when providing blood products to neonatal recipients or recipients of HPSC transplantations.

However, as noted earlier, a landmark randomized comparison of leukoreduced versus CMV-seronegative blood components in CMV-seronegative HSCT recipients (with seronegative donors) found no significant difference in the incidence of CMV infection, and CMV disease as a composite outcome and most transplantation centers [7, 15].

In practice, prestorage leukoreduced blood components will be used for CMV prevention. Other institutions simply use leukoreduced blood products in all recipients, regardless of CMV status. The latter strategy has the additional advantage of reducing the risk of alloimmunization to HLA antigens and thus of developing refractoriness to platelet transfusions.

6.9 Parasites

Malaria: malarial transmission by transfusion is common in malarial endemic regions of Africa. In nonmalarial endemic areas, donors with a history of residence in a malaria-endemic area or travel associated with a risk of malarial exposure are deferred for up to 3 years, depending on the exposure.

Chagas disease: Trypanosoma cruzi parasites can survive several weeks of storage in blood, and contamination of blood products with this organism is already a significant problem in parts of South America. Therefore, the immigration of individuals from South America to the United States raises concerns that Chagas disease may emerge as a common transfusion-transmitted infection [7, 15].

An FDA-approved blood donor-screening test for antibodies to *T. cruzi* is available. Blood donors only need to be tested at their first donation.

Babesiosis: this has been identified in receiving platelets, refrigerated RBCs, and even frozen-thawed RBCs. Cases have been reported in New England and the upper Midwest. Various tests are being evaluated for donor screening in areas endemic for Babesia [7, 15].

7. Conclusions

This chapter serves as a synopsis to adverse blood reactions which are very common but apparently more often under-recognized and/or under-reported particularly in developing countries. This should sharpen the consciousness of all health practitioners involved in blood transfusion services towards taking measures at preventing transfusion reactions right from donor selection up to the infusion of blood into the recipients.

Conflict of interest

No conflict of interest.

Notes/Thanks/Other declarations

Chapter 12; Transfusion medicine: American Society of Hematology Self-Assessment Program served as a good template on which this chapter is built.

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