Chapter 13
ADVERSE TRANSFUSION EVENTS

PRACTICE POINTS

• The most common severe reaction is ABO incompatibility caused by mis-identification or mis-labelling of the blood component, patient or pre-transfusion sample.

• Patients receiving a transfusion should be observed prior to, within 15 minutes of commencing, at the conclusion and within 1 hour after a transfusion.

• If in doubt, stop the transfusion and give IV fluids.

• Always perform blood culture and culture of the residual blood component after a high fever.
Adverse transfusion reactions that may develop during or following transfusion of a blood component are divided into acute and delayed. See Annex 5 for tables of symptoms, diagnoses and management.

Acute adverse events occur during a transfusion or within 6-12 hours of a transfusion. Symptoms and signs include:
- fever and/or chills,
- rash,
- dyspnoea,
- anxiety,
- urticaria,
- changes in blood pressure,
- tachycardia, and
- haemolysis (dark urine, pallor).

Delayed reactions may be asymptomatic, such as development of an allo-antibody and early stages of a transfusion transmitted infection. Haemolysis, neutropenia and bleeding problems are uncommon features of other delayed reactions (see Table 13.1).

If an acute transfusion reaction occurs, first stop the transfusion then check the blood pack labels and the patient’s identity. If there is any discrepancy, do not restart the transfusion and consult the blood bank. In order to rule out any possible identification errors in the clinical area or blood bank, stop all transfusions in the same ward or operating room until they have been carefully checked. In addition, request the blood bank to stop issuing any blood for transfusion until the cause of the reaction has been fully investigated and to check whether any other patient is receiving transfusion, especially in the same ward or operating room, or at the same time.

For the signs and symptoms, possible causes and management of the three broad categories of acute transfusion reaction to aid in immediate management see below.

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13.2 Management, investigation and recording acute transfusion reactions

1. Stop the transfusion and keep the IV line open with 0.9% sodium chloride while making an initial assessment of the acute transfusion reaction and seeking advice.

2. Treat symptoms on the basis of presumed diagnosis.
   a. Adrenaline, corticosteroids and anti-histamines for anaphylactic and allergic reactions.
   b. Acetaminophen (paracetamol) for fever.
   c. Antibiotics after blood culture has been taken for suspected bacterial infection.
   d. IV fluid resuscitation, respiratory support including oxygen and possibly dialysis for acute haemolysis.
   e. IV fluids for hypotensive reactions.
   f. Oxygen for respiratory distress.

3. Immediately report all acute transfusion reactions, with the exception of mild urticarial reactions, to a medical officer and to the blood bank that supplied the blood.

4. Record the following information on the patient’s notes:
   - type of transfusion reaction,
   - length of time after the start of transfusion that the reaction occurred,
   - volume and type of blood products transfused, and
   - unique donation numbers of all products transfused.

5. Immediately when the reaction occurs, take the following samples and send with a request form to the blood bank for laboratory investigations:
   - immediate post-transfusion blood samples (1 clotted and 1 anticoagulated: EDTA) from the vein opposite the infusion site, 
   - blood culture in a special blood culture bottle, if septic shock due to a contaminated blood unit is suspected, and
   - the blood unit and giving set containing red cell and plasma residues from the transfused donor blood the first specimen of the patient’s urine following the reaction.

6. Complete a transfusion reaction report form.

7. After the initial investigation of the transfusion reaction, send the following to the blood bank for laboratory investigations:
   - blood samples (1 clotted and 1 anticoagulated: EDTA) taken from the vein opposite the infusion site 12 hours and 24 hours after the start of the reaction, and
   - a patient’s urine sample within at least 24 hours after the start of the reaction.

13.3 SPECIFIC ADVERSE TRANSFUSION EVENTS

13.3.1 FEBRILE NON-HAEMOLYTIC TRANSFUSION REACTION (FNHTR)

Fever of > 1°C from pre-transfusion temperature is most commonly due to FNHTR.

Bacterial contamination and acute haemolytic transfusion reactions need to be excluded.

The fever may be accompanied by chills (cold shivers), nausea and vomiting.

13.3.1.1 Cause

This reaction is non-haemolytic and is usually caused by the presence of leucocytes or cytokines in the transfused blood. Recipient antibodies to donor leucocytes can also cause FNHTR. Such adverse reactions are unpleasant but transient.

Fever during or shortly after transfusion is less commonly caused by transfusion of incompatible blood or bacterial contamination of the blood product. See bacterial contamination.

13.3.1.2 Action

- Stop transfusion.
- Give symptomatic relief e.g. acetaminophen (paracetamol) for fever and pethidine (meperidine) for rigors.
- Maintain IV access with 0.9% NaCl (normal saline).
- If there is any doubt about the diagnosis, investigate and manage according to the bacterial contamination or acute haemolysis protocols.

13.3.1.3 Future policy

Some patients experience recurrent FNHTR. Leucocyte depletion of erythrocyte and platelet products within 24 hours of collection reduces FNHTR and is the most effect prophylaxis. Bedside leucodepletion (bedside filtration) is less effective.
but still very useful.

Pre-medication with acetaminophen (paracetamol) has not been shown to be effective. Antihistamines have no role in treatment or prevention.

13.3.2 ALLERGY: ITCHING, URTICARIA, GLOTTIS OEDEMA, ANAPHYLACTIC SHOCK

13.3.2.1 Cause

The majority of allergic reactions are unexplained. These reactions maybe caused by antibodies in the patient against plasma proteins of the donor, most commonly in a recipient who is IgA deficient and has developed an anti-IgA antibody. Other causes include the presence of allergens or cytokines in the blood product.

13.3.2.2 Action

Itching and/or urticaria

In general the transfusion should be stopped as urticaria may precede a more severe allergic reaction. Administer antihistamines

Glottis oedema and/or anaphylactic shock:

Stop transfusion immediately. Do not restart. Administration of antihistamines, corticosteroids adrenaline, vasopressors and supportive care as required.

• Investigation: IgA and anti-IgA in the patient.

13.3.2.3 Future policy

In case of anti-IgA: washed erythrocytes and platelets or use of donations from known IgA deficient donors. Consultation with the blood provider is essential. In case of repeated anaphylactic shock, consider use of washed erythrocytes or platelets.

Antihistamines and/or corticosteroids prior to transfusion may be useful for repeated moderate-severe allergic reactions.

13.3.3 ACUTE HAEMOLYTIC TRANSFUSION REACTIONS (AHTR)

13.3.3.1 Cause

Acute haemolytic reactions are predominantly due to ABO incompatibility. These are predominantly caused by administrative errors leading to “wrong blood in tube” and errors of patient identification. International studies confirm that AHTR due to ABO incompatibility is the most common cause of fatal transfusion reaction.

AHTR may also be caused by recipient alloantibodies to transfused red cell antigens.

In case of ABO incompatibility haemolysis signs and symptoms may appear within minutes of infusing only 5–10 mL of blood. Close observation at the start of the infusion of each unit is essential. The reaction will last for several hours and may be fatal.

In case of allo-antibodies against erythrocytes the reaction may start some hours later and may last several days.

In an unconscious or anaesthetised patient, hypotension and uncontrolled bleeding may be the only signs of an incompatible transfusion.

Symptoms: warm feeling at infusion site and in the face, cold shiver, restlessness, anxiety, high fever, chest pain, pain in the limbs, dyspnoea, nausea, tachycardia, hypotension, bleeding tendency caused by disseminated intravascular coagulation (DIC), jaundice, dark urine, and impaired kidney function with oliguria/anuria.

13.3.3.2 Action

Urgent treatment is required.

• Stop transfusion immediately, leave needle in situ and commence normal saline (0.9% NaCl).

• Check pulse rate, blood pressure and temperature.

• Hypotension must be treated with fluids and vasopressors and perfusion of the kidney must be guaranteed.

• Fluid supply if necessary supplemented with mannitol 20% and/or furosimide IV to obtain a minimal urine production of 1–2 mL/kg/hour.

• Alkalisation of the urine using Na-bicarbonate is indicated. Urgent haemodialysis may be required.

• Treatment of coagulation defects and hyperpyrexia as required.

Investigations:

• Check the entire administrative procedure. Specific investigations to find the root causes may indicate system changes in order to prevent future AHTR.

• Residual blood component needs repeat ABO and RhD blood group testing.

• Patient blood should be investigated for, ABO and Rh blood groups, and screening for allo-antibodies which needs to be compared to pre-transfusion results. Repeat testing of stored
pre-transfusion sample is also essential.

- Bacteriologic cultures should be done from both patient and donor blood.
- Other laboratory investigations: Haemoglobin, LDH, bilirubin, haptoglobin, platelet count, coagulation profile, fibrinogen, fibrin degradation products (FDP), creatinin, free haemoglobin in serum and urine.

13.3.3.3 Future policy

- Prevention of administrative (human) errors.
- Compatible erythrocytes.

13.3.4 DELAYED HAEMOLYTIC TRANSFUSION REACTION

This reaction is the consequence of recipient allo-antibodies against erythrocytes which are below the level of detection at the time of antibody screening. Between 2 and 10 days after transfusion the haemoglobin decreases with jaundice, fever, spherocytosis, high LDH, positive antibody screen and sometimes haemoglobinuria.

13.3.4.1 Cause

The patient is immunised during a previous pregnancy or transfusion however the antibody titre is below the level of detection. The transfusion functions like a booster with a secondary immune response and the production of high titre antibodies after some days, resulting in haemolysis of donor erythrocytes.

13.3.4.2 Action

- Check of administrative procedure of last transfusion (Identification of patient and donor, transfusion history, type & screen report and/or cross-match etc).
- Investigation of patient’s blood for antibodies against erythrocytes before and after transfusion (direct antiglobulin test, screening against panel test erythrocytes).
- Other laboratory investigation: LDH, bilirubin, haptoglobin, free haemoglobin in serum and urine.

13.3.4.3 Future policy

Typed compatible erythrocytes. The information linked to patient data on the presence of antibodies against erythrocytes must be recorded in the blood transfusion laboratory (hospital blood bank) for the life time of the patient as well as on the blood group card and/or SOS badge.

13.3.5 TRANSFUSION TRANSMISSIBLE INFECTION (TTI) - BACTERIA

A blood component with bacterial contamination may cause bacteriemia or sepsis and require immediate intervention. Bacterial contamination is a significant risk with platelets due to their storage at room temperature.

13.3.5.1 Action

- Stop transfusion.
- Disconnect blood product as soon as possible, keep needle in situ, connect clean giving set primed with physiologic saline (0.9% NaCl).
- Check whether indeed the right blood products are transfused.
- Collect blood from the patient for repeat compatibility testing (if erythrocytes are transfused) and blood culture.
- Send all blood bags used before or during the adverse transfusion reaction to the hospital blood bank for repeat compatibility testing (if erythrocytes are transfused) and to microbiology for blood culture. Compatibility testing of erythrocyte products that are not yet used, should also be repeated.

13.3.5.2 Future policy

Bacterial testing of platelet components during manufacture.

13.3.6 TRANSFUSION TRANSMISSIBLE INFECTION (TTI) - VIRUSES, PARASITES and PRIONS

Unfortunately there is still a substantial residual risk of transmissible disease in Cambodia because:

- the prevalence of TTI markers in the community is high,
- over 80% of donors are family replacement donors, a practice which carries a statistically higher risk of TTI,
- many donors are single time donors (e.g. family replacement donors). Repeat donors have lower risk of carrying a transmissible disease due to their frequency of testing,
- there may be a substantial number of donors in a window period (infectious) due to the current reliance on serological testing rather than NAT,
- ordering of blood is largely ad hoc,
- test performance is not fully consistent and standardised, and
- confirmatory testing is not yet fully developed.
Notes: Cytomegalovirus (CMV) transmission risk is high. Over 50% of the population is seropositive (anti-CMV IgG positive) for CMV. The virus is latent in leucocytes and therefore a seropositive donor, or transfusion of non-leucodepleted blood carries a significant risk of transmission of CMV. Patients who are sero-negative for CMV, and have a compromised immune system should receive CMV safe blood products (anti-CMV negative or filtered).

Other blood transmissible diseases like malaria, toxoplasmosis, babesiosis, and Chagas disease can occur. The most common is malaria and recipients of blood components from endemic or epidemic areas should receive chemoprophylaxis.

Prions, e.g. the cause of variant Creutzfeldt-Jakob disease, can be transmissible by blood but Cambodia does not have documented human or bovine cases.

13.3.7 TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)

This is a rare and often fatal complication. Residual leucocytes in the transfusion establish a graft versus host reaction in the recipient. This is more common in immunocompromised patients, however immunocompetent patients are also at risk. The practice of transfusing HLA haploidentical blood (e.g. from a related family donor) increases the risk of TA-GVHD. Irradiation kills residual immune cells in the blood component. Irradiated blood components should be used for some patient categories (see table).

Patients requiring irradiated whole blood, erythrocytes or platelets:

- Patients with congenital immunodeficiency states.
- Intrauterine transfusions.
- Neonatal exchange transfusions.
- Patients with lymphoproliferative diseases.
- Patients undergoing bone marrow or stem cell transplants.
- Recipients of directed transfusions from family members.
- Recipients of HLA-matched platelets.
- Patients treated with purine analogs (e.g. fludarabine), purine antagonists (e.g. bendamustine), alemtuzumab and anti-thymocyte globulin.

TA-GVHD could be prevented by:

1. The use of voluntary allogeneic donor blood rather than family donors.
2. Irradiation of cellular products (on request) with at least 25 Gy (2500 rad).

13.3.8 TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)

Transfusion related acute lung injury (TRALI) may occur as commonly as 1 in 2500 transfusions and in some countries has become the leading cause of transfusion related mortality. It is defined as acute lung injury, without another cause, occurring during or within 6 hours of transfusion. Acute lung injury is characterised by increasing oxygen requirement, decreasing blood oxygenation and new changes on chest X-ray. The key differential diagnosis is fluid overload, however TRALI does not respond to diuretic therapy. This condition is probably caused by leucocyte agglutinins in donor plasma against leucocytes of the recipient.

TRALI is treated with supportive care and patients often require ventilation. Diuretics and steroids are not useful.

13.3.8.1 Future policy: Prevention

The lead theory of pathogenesis relates to the presence of anti-HLA antibodies in the transfusion against HLA in the recipient. Women, particularly after pregnancy, have a higher incidence of anti-HLA antibody. Many blood providers internationally only supply plasma collected from males in order to reduce the risk of anti-HLA antibody transmission and thereby reduce the risk of TRALI. Cambodia is not in a position to consider this strategy yet.

13.3.9 TRANSFUSION ASSOCIATED CARDIAC OVERLOAD (TACO)

Fluid overload, Transfusion Associated Cardiac Overload (TACO), may occur easily due to the oncotic nature of blood products. Patients with cardiorespiratory compromise should be closely monitored and the erythrocyte transfusion may need to run over 4 hours rather than the usual 1–2 hours. Oxygen and diuretic therapy as needed.

13.3.10 POST-TRANSFUSION PURPURA (PTP)

PTP is caused by the transfusion of platelet antigen positive blood into a recipient who does not express that antigen and has previously developed antibodies to that antigen. The most common antigens involved are the platelet specific antigens, in particular the transfusion of HLA-1a positive blood to a HLA-1b homozygous patient. Thrombocytopenia occurs 1–24 days after transfusion.

Treatment with IVIg and prevention is by transfusion of antigen negative platelets.
Alloimmunisation can occur to other platelet or neutrophil antigens in a similar manner to red cell alloimmunisation. The clinical significance of these alloimmunisations is variable.

13.3.11 COMPLICATIONS OF MASSIVE TRANSFUSION

Complications include:

- **Dilutional coagulopathy.** This can be mitigated by inclusion of plasma and fibrinogen (or cryoprecipitate) into the massive transfusion.
- **Hypothermia.** Rapid transfusion of large volumes of cold blood can cause cardiac arrhythmia and worsen core temperature fall.
- **Hypotension, worsened coagulopathy and platelet dysfunction** are all consequences of hypothermia.
- **Citrate toxicity and hypocalcaemia.** Citrate is usually metabolised rapidly in the liver, however during massive transfusion and hypothermia, this capacity may be overwhelmed. Treat tetany (muscle spasms), paraesthesias and other signs of hypocalcaemia (e.g. arrhythmias and hypotension) with 1 g calcium chloride IV (max rate 100 mg/minute). Routine use of calcium after transfusion is not required.
- **Hyperkalaemia** is more common in neonates with massive transfusion but can complicate adult massive transfusion.