

EDUCATION SESSION 10: TRANSFUSION MEDICINE



Adverse Effects of Blood Transfusion

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In the developed world, with all-voluntary donations, self-exclusion, and advanced screening assays, the risks of blood transfusion are very low, and it is therefore difficult to assess new methods for improving blood safety. Although allogeneic blood transfusion has never been safer, the perception of the public, fed by the media and some commercial companies, is that blood is becoming increasingly unsafe. Because the current serious risks of blood transfusion are so low, it is difficult to quantify them and it is practically impossible to assess new measures to increase the safety of the blood supply. On the other hand, in countries with a high proportion of paid donors or replacement donors, the microbiological risks of transfusion are much greater.

Though infrequent, there are numerous adverse effects of transfusion; minor transfusion reactions such as fever and urticaria occur in approximately 1 in 100 transfusions. The most serious hazards are (1) hepatitis or HIV infection, (2) ABO haemolytic transfusion reactions, mostly due to identification mistakes and (3) bacterial contamination. Many of these major risks are preventable, such as identification mistakes or failures to test. Examples of non-preventable risks are transmission of infection during the "window period", delayed haemolytic transfusion reactions, idiosyncratic reactions, anaphylaxis (e.g. when it is unknown that the recipient has anti-IgA), post-transfusion purpura, possibly immune modulation (?largely preventable with leucodepletion), transfusion related acute lung injury, etc.

Only a minority of recipients of ABO-incompatible blood suffer serious morbidity or mortality. It is estimated, in the USA and UK, that about 1 in 30,000 units of red cells transfused are ABO incompatible yet deaths due to ABO incompatibility are of the order of 1 in 500,000- 600,000. This fatality rate, though small, is much higher than the risk of acquiring HIV by transfusion in the UK, which is less than 1 in 2,500,000 units transfused. We continue to strive to reduce the risks of viral transmission by transfusion, yet we neglect the important areas of reducing errors of identification and bacterial contamination of red cells and, particularly platelets, leading to septicaemia or endotoxic shock, estimated conservatively to be of the order of 1-2 in 1,000,000 units transfused.

Because there are always risks associated with transfusion, blood derivatives should only be prescribed when there are no safer alternatives, such as iron therapy, volume replacement with colloids or crystalloids, and intraoperative blood salvage. Hence, transfusion should only be prescribed when the benefits outweigh the risks.

Adverse effects can be classified according to whether they are **immediate** or **delayed** and whether they are immunologically mediated or not. The various types of adverse reactions are shown in **Tables 1** and **2**.

Blood is a biological material and there will always be risks associated with the transfusion of blood, blood components, and blood products. Blood should be prescribed only when there is no safer alternative, e.g. Fe therapy, DDAVP, etc., and should never be administered without careful thought as there will never be a 'zero-risk' blood supply.

Immediate Complications

Immunological

1. Red cell incompatibility: haemolytic transfusion reactions.
 - (i) Immediate intravascular reactions (usually ABO incompatibility mostly due to clerical errors or because

Table 1. Acute or immediate complications of transfusion (occur within 1-2 hours)

Immunological:

- Haemolytic transfusion reactions (HTR) with symptoms
- Febrile, non-haemolytic transfusion reactions
- Urticarial
- Anaphylactic
- Transfusion-related acute lung injury (TRALI)

Non- Immunological:

- Bacterial contamination with/without endotoxic shock
- Congestive cardiac failure
- Hypothermia
- Haemolysis without symptoms (haemolysed blood transfused)
- Embolism
- Hyperkalaemia
- Hypocalcaemia

Table 2. Delayed complications of blood transfusion*
(Occur days, weeks or months after transfusion)

Immunological:

Delayed haemolytic transfusion reactions (DHTR)
Post-transfusion purpura
Graft-versus-host disease
Delayed serum sickness-type reactions

Non-Immunological, mainly infectious:

Hepatitis: B
C
A (rare)
Other non-A, non-B
HIV infection Babesiosis
CMV infection Brucellosis
Malaria Trypanosomiasis (Chagas' disease)
Syphilis Parvovirus

* New variant CJD (nvCJD), the equivalent of BSE in cattle ('mad cow disease') has never been reported to be transmitted by transfusion. However, because the abnormal prion is present abundantly in the lymphoreticular system of those few patients diagnosed with this disease and who have died, the UK has taken serious and expensive measures to prevent the 'hypothetical' risk of prion transmission by transfusion.

the patient is given blood intended for another patient. They are caused by complement fixing IgM antibodies such as anti-A,B in a group-O patient transfused in error with group A or B blood).

(ii) Immediate extravascular reaction (immune antibodies, mainly Rh, e.g. D-negative patient with anti-D, given RhD positive blood by mistake).

2. **Simple febrile reactions** (0.5–1% of transfusions) mostly due to anti-white cell antibodies (present in those who have been pregnant or transfused previously). Manifest as rise in temperature, sometimes headache, nausea, rigor, usually at end of transfusion or after a few hours. Rarely severe. Treat with anti-pyretics, antihistamines, hydrocortisone, etc and slow transfusion rate. If severe or recurrent, use white cell-depleted blood, though for the vast majority of cases, buffy coat-poor red cells will suffice.
3. **Allergic reactions** due to anti-protein antibodies, range from urticaria to anaphylactic reactions. Most commonly simple urticaria. Not dangerous. Treat with antihistamines. Very rarely severe anaphylactic shock, hypotension, wheeze, etc. in IgA-deficient patients with anti-IgA. Treat with steroids, adrenaline, supportive therapy.
4. **Transfusion-related acute lung injury (TRALI):** if the donor's plasma contains potent WBC-antibodies (leukoagglutinin) incompatible with the recipient's leucocytes, TRALI may result in congestive cardiac failure (CCF). Multiparous women often develop antibodies against paternal antigens on fetal WBC; it is these antibodies which are responsible for most reported cases of TRALI. This is a very uncommon transfusion reaction; more commonly CCF results from fluid overload.

Non-immunological

1. **Bacterial infection:** contamination of blood at source (during collection) or due to faulty storage. Some organisms will grow slowly in blood stored at 4°C. If blood is allowed to warm up, bacterial growth increases and septicaemia may develop. Hence the importance of correct storage of blood in controlled refrigerators. Bacterial infections are more frequent after platelet transfusions due to the storage requirements of platelet concentrates at room temperature.
2. **Dangers of i-v therapy:** thrombophlebitis, circulatory overload etc.
3. **Haemolysis:** giving blood with hypotonic solution or through very small needle, or inappropriate warming/cooling.
4. **Hypothermia:** giving large volumes of blood at 4°C may lead to DIC in small babies.
5. **Embolism** due to clots, aggregates or extraneous material. Therefore mandatory to use a blood giving set with an integral filter (170 mm).
6. **Hyperkalaemia:** from haemolysis during storage, only of importance when >1 blood volume replaced, especially in infants.
7. **Hypocalcaemia:** the citrate anticoagulant binds Ca⁺⁺ and may lead to transient hypocalcaemia. Ca⁺⁺ mobilised from bone therefore usually no clinical consequences and no treatment is required.
8. **Metabolic disturbance:** rare unless massive transfusion of blood.

Delayed Complications

Immunological

- (i) **Delayed haemolytic transfusion reactions (DHTR):** this is extravascular destruction of red cells caused by IgG red cell alloantibodies not detectable in the patient before transfusion. However, the patient has been primary immunised ('primed') and on re-encountering the antigen, develops an anamnestic immune response (e.g. anti-D, anti-K, -Fy^a, -Jk^a etc.) which occurs 3-10 days after transfusion. DHTRs are usually seen as a post-transfusion drop in haemoglobin and rise in serum bilirubin.
- (ii) **Alloimmunisation** to red cell or white cell (HLA) antigens. Occurs in 1-2% of patients who receive compatible transfusions. Alloimmunisation results in the development of antibodies later but is not harmful per se.
- (iii) **Post transfusion purpura (PTP):** very rare, occurs when platelet antibodies develop as a secondary response and destroy their transfused incompatible platelets.
- (iv) **Transfusion associated graft-vs-host disease (GVHD):** may be acute or chronic and results from viable lymphocytes from transfused blood or platelets engrafting in an immuno-incompetent patient, i.e. transfusion following whole body irradiation for bone marrow transplantation, fetal transfusions, and in a few diseases causing severe immunosuppression like Hodgkin's disease

and congenital immunodeficiency states. These patients should be given blood components irradiated to destroy lymphocyte viability.

- (v) **Immunosuppression/immunomodulation**: some recent evidence that blood transfusions are immunosuppressive, e.g. bacterial infections distant from the site of operation commoner when patient receives allogeneic blood during surgery.

Non immunological

1. **Iron Overload**. 1 unit of blood contains approx 250 mg iron. Accumulation occurs especially in patients receiving long-term transfusion therapy, e.g. β -thalassaemia major.
2. **Transmission of infection**: risk depends on:
 - (i) Prevalence of the infectious agent in the population.
 - (ii) The effectiveness of excluding potential infectious donors, eg high risk groups.
 - (iii) Screening of blood for infectious agents
 - (iv) Processes to sterilise certain products, e.g. Albumin, Factor VIII.

In the UK it is mandatory to test every donation for hepatitis B and C, HIV 1 + HIV 2, and syphilis. If there is a risk of transmission of malaria, donations are tested for malarial antibodies.

- (i) **Hepatitis B**: rare, but more common than HIV. Not usually lethal. Not totally preventable. All donations screened for Hepatitis B surface antigen (HBsAg) but it is possible for individuals to be infectious through blood transfusion when the level of virus is below the level of detectability of current tests.

Reduced since measures for HIV transmission introduced, i.e. same risk factors (male homosexuals, IV drug abusers).

In the Far East, transmission of virus from mother to child is commonest cause of infection.

- (ii) **Hepatitis non A, non B**: Probably more than one causative agent, one of which is the hepatitis C virus (HCV). Rarely lethal but can lead to chronic liver disease. Transfusion-transmitted infection was more common than hepatitis B (10% of all transfusions in USA, probably less in UK). Now that blood is tested for anti-HCV, risk is significantly lower.
- (iii) **HIV**: two viruses recognised, HIV1 and HIV2. Routine screening of all blood donations for HIV1/2 antibodies; some countries (e.g. USA, Thailand) test for HIVp24 antigen.

Also donor education, self-exclusion of "high risk" individuals.

Transmission now virtually restricted to those few donors who are in early infectious stage but have not yet developed the antibody ("window period").

Current pick up rate of anti-HIV-I in UK blood donors: 1 in 100,000.

- (iv) **Cytomegalovirus**: only a problem in immuno-suppressed patients.

55% of adult blood donors are immune and therefore potentially infectious (latent infection).

Patients at risk: fetuses and low birthweight premature babies, transplant recipients, and other patients who receive immunosuppressive therapy (irradiation), and severely immunodeficient patients.

Seronegative patients in these groups are provided with CMV-screened red cells/platelets or with leuco-depleted cellular components.

Transfusion per se may reactivate latent intracellular virus in the recipient.

- (v) **Syphilis**: very rare but routine blood donor screening still used (very useful surrogate test which detects population at risk of other sexually transmitted infections (STDs).

- (vi) **Malaria**: very rare in non-endemic areas, but increasing foreign travel has exposed more people so screening for malaria antibodies of selected donors used in some areas of the UK.

Key References

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