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Chapter 14

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Blood Transfusion

Only 39% of the global blood supply is donated in the poorest countries where 82% of the world's population lives.[1]

Blood transfusion is a vital component of every country's health service (Table 14.1). It can be a life-saving intervention for severe, acute anaemia, but mistakes in the transfusion process can be life-threatening, either immediately or years later through transmission of infectious agents. It is imperative that clinicians have a good understanding of how blood is acquired and prepared for transfusion, and when it should be used, and that governments put in place quality assurance mechanisms to guarantee that blood for transfusion is safe.

BLOOD TRANSFUSION SERVICE AT THE NATIONAL LEVEL

Transfusion medicine is critical to the success of most clinical specialties and should be incorporated into all national health plans and budgets. Only 16% of member states meet all the World Health Organization's (WHO) recommendations for a national quality blood transfusion system.[1] At the national level the transfusion service should have a director, an advisory committee and clear transfusion policies and strategies (Table 14.2). Blood collection, testing and distribution need to be standardized. Although centralization of these services may offer the best guarantee of quality, it is often not practical in countries with poorly developed communications and transport infrastructure. In such countries, each hospital organizes its own blood transfusion service and it is then difficult to ensure national standardization and quality. Hospital-based transfusion services place an enormous burden on laboratory resources and on the families of patients because they are responsible for finding suitable blood donors. In a typical district hospital in Malawi, the overall cost of the transfusion service, including consumables, proportional amounts for capital equipment, staff time and overheads, was 53% of total laboratory costs and each unit of whole blood cost the laboratory approximately £10 to collect and process.[2]

In wealthy countries with nationally or regionally centralized transfusion services, blood donor recruitment, and screening and processing of donated blood, are carried out in purpose-built centres which are separate from the hospitals where the blood is transfused. These centres operate to good manufacturing standards similar to those laid down for the pharmaceutical industry. After donation and exclusion of potentially infected units, the blood is separated into components and filtered to remove white cells. Computerization enables individual components to be barcoded so they can be tracked back to the original donor. Hospitals are proficient at predicting how much blood they will require and they receive regular consignments through a well-established delivery network. The efficiency of the system means that one donor centre may provide blood to many hospitals and cover a population of several million. This process is expensive and one unit of blood currently costs over £100.[3]

Separation of whole blood into components

In wealthy countries it is standard practice to optimize the use of each donation of blood by separating it into individual components. These components, which may include plasma, platelets and cryoprecipitate, are prepared by centrifugation using a closed, sterile system. Each component has different storage requirements. Plasma and cryoprecipitate are kept frozen, red cells are stored at 1–5°C, and platelets at 18–22°C with constant agitation. Separation of blood, even into simple components such as cells and plasma, requires equipment and expertise, so in the poorest countries blood components may only be accessible to those living close to a central hospital with blood separation facilities.

Ensuring safety of blood for transfusion

An unsafe blood supply is costly in both human and economic terms. Transfusion of infected blood causes morbidity and mortality in the recipients, and has an economic and emotional impact on their families and communities. Those who become infected through blood transfusion are infectious to others and contribute to the spread of disease throughout the wider population. This increases the burden on health services and reduces productive labour.

Selecting low-risk blood donors

Strategies for recruiting blood donors have to balance supply with demand, and yet ensure that the blood is as safe as possible. In

general, the safest sources of blood are altruistic voluntary unpaid donors who should be anonymous to the recipient. Only 32% of WHO member states report having at least 90% of their blood supply from voluntary donors, and developing countries have not shown any improvement in recruitment of voluntary donors for several years.[1]

In countries without a national transfusion service, each hospital is responsible for finding its own donors and processing blood for transfusion. Recruiting voluntary donors from the community is expensive and logistically complicated, requiring resources such as a local education programme, dedicated venesection team, vehicles and cold storage. Paid donors or 'loan' systems, where family members are responsible for providing blood for their relatives in the hospital, are therefore widespread in poorer countries. Cultural taboos and misinformation about donating blood (e.g. 'men will become impotent if they donate blood'; 'HIV can be caught from the blood bag needle') mean that relatives may be reluctant to donate. Families are open to exploitation by 'professional donors' who charge a fee to donate in place of a family member. By the time a donor has been found, screened and venesected, and the blood is transfused into the patient, several hours or even days can elapse, especially if blood of a rare group is required. Because patients in poorer countries often present late in the course of their disease, severely anaemic patients may die in hospital without ever receiving a blood transfusion. It is unfortunate that in many countries where the majority of transfusions are performed as an emergency and where it is imperative to have a well-stocked blood bank, the 'loan' system, with its inherent delays, predominates.

Potential 'high-risk' donors, such as commercial sex workers or those having frequent contact with these individuals, intravenous drug abusers, or persons with itinerant or fluctuating activities such as traders, drivers and military personnel, should be permanently deferred from the donor pool.[4] Even in areas where HIV infection rates in the general population are high, donor deferral can be effective in excluding HIV-infected donors.[5] The whole donation process, including tests for HIV and other infections, should be explained to the donor before blood is collected and donors should have the option of knowing the results and receiving counselling. It is imperative that complete confidentiality is maintained throughout all procedures.

Table 14.1 Global facts about blood transfusion

80% of the world's population has access to 20% of the world's safe blood supply
Transfusion or injection of unsafe blood accounts for 8–16 million hepatitis B virus infections, 2.3–4.7 million hepatitis C virus infections, and 80 000–160 000 HIV infections each year
25% of maternal deaths from pregnancy-related causes are linked with blood loss

Screening for transfusion-transmitted infections

Infections with organisms that are common in tropical countries, such as HIV-1 and -2, hepatitis A, B, C and D, cytomegalovirus, syphilis, lyme borreliosis, malaria, babesiosis, American trypanosomiasis (Chagas' disease) and toxoplasmosis, can all be acquired through blood transfusions. There have also been recent reports of transmission of variant Creutzfeldt–Jakob disease through blood transfusion and there is a theoretical risk of acquiring severe acute respiratory syndrome (SARS) through transfusion of labile blood products.[6,7] WHO recommends that all donated blood should be screened for HIV, hepatitis B and syphilis and, where feasible and appropriate, for hepatitis C, malaria and Chagas' disease.

Between 5% and 10% of HIV infections worldwide are thought to have been transmitted through the transfusion of infected blood and blood products. HIV testing of blood donors needs to be highly sensitive, and blood which tests positive should be rejected. Before informing the donor of the outcome, all positive results should be confirmed using a test with a high degree of specificity. Where blood donation is organized locally, the confirmatory test is often performed at a central laboratory, so there may be delay in informing the donor of the result.

Malaria can be transmitted by transfusion and has an incubation period of between 7 and 50 days, depending on the species. In areas of low or no malaria transmission, screening for the parasite is important, as recipients are likely to have no immunity. In countries with high malaria transmission, exclusion of parasitaemic donors could result in deferral rates exceeding 30% and consequently would have a major impact on blood supply.[8] It is unclear whether malaria screening is necessary in regions where

Table 14.2 Elements and national strategies for blood safety[1]

Essential element	Supporting strategy
Well-organized, nationally coordinated blood transfusion service	Government commitment; specific, adequate budget; implementation of national blood policy and plan; legislative and regulatory framework
Quality systems covering all aspects of activities	Organizational management; quality standards; documentation systems; staff training; quality assessments
Blood collection only from voluntary, non-remunerated donors	Effective donor recruitment programmes; stringent donor selection criteria; donor care programme
Quality assured testing of all donated blood	Testing for transfusion-transmissible infections; accurate blood group serology and compatibility testing procedures
Reduction in unnecessary use of blood	Use of appropriate component therapy; safe administration of blood and blood products

the disease is common, particularly because most of the blood is given to hospitalized children with malaria who are likely to be receiving antimalarial drugs, or adults who are clinically immune. Further research to assess the risks and benefits of screening blood for malaria is needed, particularly in relation to pregnant women and patients with HIV infection.

Screening for hepatitis B surface antigen should be carried out on all donated blood, as hepatitis B-infected blood is almost 100% infectious. Fresh blood is potentially infectious for syphilis, but storage at 4°C can inactivate *Treponema pallidum*. Globally, the prevalence of hepatitis C, HTLV-1 and -2 and Chagas' disease is variable and the decision to introduce donor screening for these infections will be based on local assessments of the risks, benefits, feasibility and costs. Blood should not be separated into components if the residual risk of infection is high, as this will increase the number of potentially infected recipients. In some wealthy countries nucleic acid amplification techniques (NAT) have been introduced to improve the safety of blood. Although NAT may not be cost-effective where infection prevalence is low, it has reduced the residual risk for HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV) infection in Germany to 1 in 5 540 000, 1 in 4 400 000 and 1 in 620 000, respectively.[9]

Blood is usually taken from donors and stored in a blood bank until screening tests for infections have been completed. This system has several drawbacks: potentially infected blood may be mixed up with units that have already been screened, and the whole process of venesection with wastage of blood collection bags is costly. Pre-donation screening, by which potential donors are tested for HIV, hepatitis B and possibly hepatitis C at the site of donation before being venesected, may be a more cost-effective way of ensuring safe blood.[10]

CLINICAL USE OF BLOOD

Reasons for transfusion in poorer countries

In wealthy countries the majority of transfusions are planned and carried out electively. By contrast, in poorer countries, and particularly those where the malaria transmission rate is high, most transfusions are given for life-threatening emergencies. In these countries 50–80% of transfusions are administered to children, predominantly for malaria-related anaemia. Transfusion can significantly reduce the mortality of children with severe anaemia but it may not have any benefit unless it is given within the first 2 days of hospital admission.[11] In areas of high HIV prevalence, young children have a relatively low risk of being infected with HIV and potentially have a long life expectancy. However, this is the age group that is predominantly affected by severe malaria-related anaemia and so they are particularly at risk of transfusion-acquired HIV infection.[12] Pregnant women are the second most common recipients of blood, particularly for haemorrhagic emergencies.[13] Other specialities which are significant users of blood are surgery, trauma and general medicine.

Avoiding unnecessary transfusions

Whether a patient needs a blood transfusion or not is ultimately a clinical decision. Emergency transfusions can be life-saving for patients in whom the anaemia has developed too quickly to allow physiological compensation. Examples of such emergencies include severe malaria-related anaemia in children, and sudden, severe obstetric bleeding. In contrast, if the anaemia has developed slowly, for example due to hookworm infestation or nutritional deficiency, patients can generally be managed conservatively by treating the cause of the anaemia and prescribing haematinic replacements. These should be continued for at least 3 months after the haemoglobin has returned to normal, so that body stores can be replenished.

Guidelines for transfusion practice

It is possible to avoid unnecessary transfusions through the use of clinical transfusion guidelines, and most institutions or organizations have developed guidelines to help clinicians make rational decisions about the use of blood transfusions (Table 14.3).[14] Strict enforcement of a transfusion protocol in a Malawian hospital reduced the number of transfusions by 75% without any adverse effect on the mortality rate.[15] While the details may vary, the principles underlying most transfusion guidelines are similar and combine a clinical assessment of whether the patient is developing complications of inadequate oxygenation, with measurement of their haemoglobin. The haemoglobin level is used as a surrogate measure for intracellular oxygen concentration. Increasingly, transfusion guidelines are making use of evidence which shows that adequate oxygen delivery to the tissues can be achieved at haemoglobin levels that are significantly lower than the normal range.[16]

Table 14.3 Prescribing blood: a checklist for clinicians[14]

Always ask yourself the following questions before prescribing blood or blood products for a patient:

1. What improvement in the patient's clinical condition am I aiming to achieve?
2. Can I minimize blood loss to reduce this patient's need for transfusion?
3. Are there any other treatments I should give before making the decision to transfuse, such as intravenous replacement fluids or oxygen?
4. What are the specific clinical or laboratory indications for transfusion in this patient?
5. What are the risks of transmitting HIV, hepatitis, syphilis or other infectious agents through the blood products that are available for this patient?
6. Do the benefits of transfusion outweigh the risks for this particular patient?
7. What other options are there if no blood is available in time?
8. Will a trained person monitor this patient and respond immediately if any acute transfusion reactions occur?
9. Have I recorded my decision and reasons for transfusion on the patient's chart and the blood request form?

Finally, if in doubt, ask yourself the following question:

If this blood were for myself or my child, would I accept the transfusion under these circumstances?

It is easier to develop guidelines than to ensure that they are used in routine practice. Implementation of transfusion guidelines is particularly difficult if clinicians do not have confidence in the quality of haemoglobin measurements. It has been shown that when doubtful of the quality of haemoglobin result, clinicians rely entirely on clinical judgement to guide transfusion practice. This may lead to significant numbers of inappropriate transfusions.[17] In a typical district hospital in Africa, the cost of providing a unit of blood through the family 'loan' system is approximately 30 times the cost of a quality-assured haemoglobin test. A lack of investment in assuring the quality of a basic but critical test such as haemoglobin measurement can result in a significant waste of resources downstream in the transfusion process, with the additional unnecessary exposure of recipients to the risk of transfusion-related infections.

Haemoglobin thresholds for transfusion

In resource-poor countries, the recommended haemoglobin threshold for transfusions is often well below that which would be accepted in more wealthy countries. For example, American anaesthetists suggest that transfusions are almost always indicated when the haemoglobin level is less than 6 g/dL,[18] whereas in Malawi transfusions are recommended for children with haemoglobin levels less than 4 g/dL, provided there are no other clinical complications.[19] Complications such as cardiac failure or infection may necessitate transfusion at a higher haemoglobin level. Transfusion should be combined with adequate iron and folate replacements and treatment of any underlying conditions that contribute to anaemia, so that a normal haemoglobin count can be achieved during the weeks following transfusion.

Any transfusion service must be able to guarantee the quality of haemoglobin results. These results are crucial in donor selection and are also used to guide the decision to transfuse patients. Although it is the most commonly performed test, accurate haemoglobin estimation is difficult to achieve in laboratories without automated blood analysers.[20] The reference technique for haemoglobin measurement is the haemiglobincyanide method. Not only does this method need a constant electricity source for the spectrophotometer, but also technicians need arithmetic expertise to calibrate the equipment and automatic pipettes for accurate measurements. In under-resourced countries, district hospitals may use simpler, cheaper and less accurate methods of haemoglobin measurement, many of which are based on visual colour comparisons. While a few individual laboratories in resource-poor countries may be registered with an external system to monitor the quality of laboratory tests, almost no country has a nationwide programme. This means that for many laboratories and their users, the quality of tests, including haemoglobin and those used for screening and determining blood groups, is unknown.

COMPLICATIONS OF BLOOD TRANSFUSION

Complications can occur immediately during transfusion, within a few hours of its completion, or be delayed for many years, as in the case of viral infections. See Table 14.4.

Table 14.4 Complications of blood transfusion

- Febrile non-haemolytic transfusion reactions. Haemolytic reactions include chills, headache, backache, dyspnoea, cyanosis, chest pain, tachycardia and hypotension
- Risk of severe bacterial infection and sepsis
- Transmission of viral infection (hepatitis B, HIV or hepatitis C)
- Transmission of blood-borne trypanosomes, filaria, malaria, etc.
- Cardiac failure
- Air embolism
- Transfusion-associated acute lung injury (TRALI) – a syndrome of acute respiratory distress, often associated with fever, non-cardiogenic pulmonary oedema, and hypotension, which may occur as often as 1 in 2000 transfusions
- Other risks: volume overload, iron overload (with multiple red blood cell transfusions), transfusion-associated graft-versus-host disease, anaphylactic reactions (in people with IgA deficiency), and acute haemolytic reactions (most commonly due to the administration of mismatched blood types)

Acute and delayed haemolysis due to red cell incompatibility

Transfusion of blood into a recipient who possesses antibodies to the donor's red cells can cause an acute, and occasionally fatal, intravascular haemolysis. This could occur, for example, if group A cells are transfused into a group O recipient who has naturally occurring antibodies to group A cells. The profound haemolysis induces renal vasoconstriction and acute tubular necrosis. Treatment involves stopping the transfusion, cardiorespiratory support and inducing a brisk diuresis. In addition to abnormalities indicating renal failure, laboratory findings include haemoglobinuria and haemoglobinaemia. Proof of the diagnosis involves rechecking the whole transfusion process including all documentation stages, regrouping the donor and the recipient, and screening for antibodies on red cells with a direct antiglobulin test. These tests are usually available in any hospital laboratory capable of providing a transfusion service. Delayed haemolysis has a similar physiological basis to acute intravascular haemolysis but tends to be less severe. The antibody–antigen reaction develops 7–10 days after the transfusion and it is less likely than acute haemolysis to present as a clinical emergency.

Bacterial contamination

Bacteria can enter the blood bag during venesection or if the bag is perforated at a later stage, perhaps to reduce the volume for a paediatric recipient or during component preparation. Gram-negative bacteria, including *Pseudomonas* and *Yersinia*, grow optimally at refrigerator temperatures and infected blood may not necessarily appear abnormal. Reactions following infusion of infected blood are often due to endotoxins and may occur several hours after the transfusion has finished. Although these reactions are rare, they can be severe and fatal. If bacterial contamination is suspected, the transfusion should be stopped and samples from

the patient and the blood bag sent to the laboratory for culture. Cardiorespiratory support may be needed and broad-spectrum antibiotics should be started immediately and continued until culture results are available.

Non-haemolytic febrile reactions

These are episodes of fever (i.e. ≥1°C rise in temperature) and chills for which no other cause can be found. They are due to the recipient's antibodies reacting against antigens present on the donor's white cells or platelets. These reactions are most common in patients who have received multiple transfusions in the past and have therefore been exposed to a broad range of antigens. Mild febrile reactions usually respond to simple antipyretics such as paracetamol. More severe reactions may be the first indication of a haemolytic transfusion reaction or bacterial contamination and should be investigated and managed accordingly.

Allergic reactions

These are due to infusion of plasma proteins and manifestations include erythema, rash, pruritus, bronchospasm and anaphylaxis. The transfusion should be stopped and the patient treated with antihistamines. If the reaction is mild and the symptoms and signs completely disappear, the transfusion can be restarted. If this type of mild reaction occurs repeatedly with more than one unit of blood, the red cells can be washed before transfusion. This should only be done if absolutely necessary, as it carries the risk of introducing potentially fatal bacterial infection. Severe allergic reactions with evidence of systemic toxicity should be managed as acute anaphylaxis.

Circulatory overload

Blood should always be transfused slowly, to avoid overloading the circulation, unless the patient is actively and severely bleeding. Overload may be a particular problem when paediatric blood bags are not available, as children may be over-transfused due to miscalculation of the required volume, lack of accurate infusion devices or inadvertent administration of an adult-sized unit of blood.

Transfusion-transmitted infections (see above)

In tropical practice, blood transmission of hepatitis B, HIV-1 and -2, and, in some areas, American trypanosomiasis (Chagas' disease) is of particular concern. In general, transfusions are not the major route of transmission of these infections and they may not cause clinical problems until many months or years after the transfusion.

Haemosiderosis

Four units of blood contain the equivalent of the amount of iron stored in the bone marrow (approximately 1 g). Repeated transfusions for chronic haemolytic anaemia, as in thalassaemia major and sickle cell disease, lead to iron deposition in parenchymal cells. Eventually, failure of the heart, liver and other organs supersedes. Adequate doses of iron chelators, such as injectable desferrioxamine or the newer oral chelator, deferiprone, are able to maintain acceptable iron balance in patients with chronic anaemia receiving regular transfusions.

Hypothermia

It is not usually necessary to warm blood unless rapid transfusion of large quantities is needed. This may lower the temperature of the sino-atrial node to below 30°C, at which point ventricular fibrillation can occur. If blood needs to be warmed, an electric blood warmer specifically designed for the purpose should be used. This keeps the temperature below 38°C, thereby avoiding the haemolysis associated with overheating blood.

Graft-versus-host disease

Graft-versus-host disease occurs when donor lymphocytes engraft in an immune-suppressed recipient. The lymphocytes recognize the recipient's bone marrow as foreign and induce aplasia. Graft-versus-host disease is almost universally fatal and can be prevented by irradiating the donor blood, which inactivates the donor lymphocytes.

REDUCING THE USE OF BLOOD TRANSFUSIONS

Minimizing surgical blood loss

Where blood is in short supply, it is particularly important to ensure that the best anaesthetic and surgical techniques are used, to minimize blood loss during surgery. Drugs which improve haemostasis or reduce fibrinolysis, such as aprotinin and cyklokapron, and fibrin sealants, can be effective in reducing perioperative blood loss and hence the need for blood transfusion. Cost is a major limiting factor to the use of these therapies in poorer countries, and surgical blood loss is generally not a major contributor to the overall transfusion needs.

Preoperative autologous blood deposit

Patients undergoing planned surgery who are likely to require a blood transfusion can have units of their own blood removed and stored prior to surgery for use by themselves only, if significant intraoperative blood loss is anticipated. Preoperative autologous donation can reduce the need for allogeneic transfusions by 46–74%[21] but it requires careful organization: the surgeon needs to predict how much blood will be required, the patient has to be fit enough to withstand removal of one or more units of blood over the weeks preceding the surgery (preoperative haemoglobin will drop by about 1 g/dL), and the surgery must take place within the shelf-life of the blood. As the blood has to be stored in the blood bank there is still a risk that the patient may receive blood which is not his or her own or that the blood may become infected with bacteria during the process.

Intraoperative blood salvage

This involves collecting blood lost during the operation and reinfusing it into the patient either during or after surgery. Although

this technique is practical and safe, and reduces the need for donor blood by 27–53%,[21] it requires specialized equipment and training and may be more expensive than routinely donated blood.[22]

Other methods

Normal saline or intravenous replacement fluids can be used judiciously in acute blood loss, and in certain circumstances may be as effective as whole blood, red cells or plasma. Erythropoietin, which stimulates endogenous red cell production, has well-established uses in chronic anaemias such as those due to renal failure, cancer and HIV infection. Its delayed action makes it unsuitable for use in acute anaemias, the major reason for transfusions in poorer countries. The development of synthetic oxygen carriers, generally perfluorocarbons, has been fraught with problems and they are not routinely available.[23]

In under-resourced countries, especially those with a heavy burden of malaria, the most effective way to avoid the need for transfusions is to reduce the prevalence of anaemia in the community. More studies on the ability and cost of combined interventions such as the provision of bed nets, nutritional supplements and anthelmintic drugs to children to prevent anaemia and reduce transfusion requirements are needed. When resources are very limited, governments may need to make some difficult decisions in order to achieve an equitable balance between investing in a transfusion service and public health measures to reduce anaemia.

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