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# Quality use of blood products

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## SUMMARY

Blood products are a valuable resource, derived from altruistic donations. They undergo high-cost screening and modification to decrease the risk of transfusion-transmitted infection.

Although blood products have achieved a high level of safety, significant risks associated with transfusion remain.

To avoid unnecessary transfusions, patient blood management involves optimising red cell mass, minimising blood loss, and optimising physiological tolerance of anaemia.

A circumspect approach to prescribing blood products is recommended. Regular patient assessment in conjunction with judicious laboratory testing are the primary considerations in the decision to transfuse.

Evidence-based guidelines for the appropriate use of blood products have been released by the National Blood Authority.

## Introduction

Providing a safe, reliable and economically viable source of blood products is a key role of the National Blood Authority, a statutory agency within the Australian Government Department of Health. The national blood supply is jointly funded by federal, state and territory governments. It costs over $1000 million annually and patients bear no direct costs for these products.[1]

Derived from altruistic donations, blood components are subjected to a series of processes to optimise their safety. These include:

- donor screening
- mandatory testing for ABO and RhD blood type
- antibody screening
- screening for transfusion transmissible infections by serological and molecular methods
- universal leucodepletion of products (by the filtration of white blood cells from all donor units)
- bacterial contamination screening of all platelet units.

These processes are expensive and the Australian Red Cross Blood Service now includes the unit cost on the product label (Table).[2] Further costs are incurred for administering blood products, taking into account pretransfusion testing, dedicated resources during administration, and the cost of investigating and treating adverse transfusion effects. These may be 3–5 times the cost of the actual blood product.[3]

Evidence-based prescribing of blood products is essential. However, wide variability in transfusion practice[4-7] reflects the relative lack of high quality data on which to base transfusion decisions. Transfusion practice is also undoubtedly influenced by institutional protocols, unit policies and personal experiences.

## Blood supply

The ageing population and the development of more intensive and specialised therapies requiring blood support have increased the demand for blood products. The majority of transfusion recipients in Australia are aged over 65 years.[8] This proportion of the population is growing in relation to the pool of donors so there is the potential for a shortfall in the blood supply.

### *Safety*

Comprehensive regulations covering all aspects of blood donation and processing of blood products mean Australian blood supplies are among the safest in the world. Governance for prescribing and clinical use have been formalised in the National Safety and Quality Health Service Standards.[9]

Risks associated with blood transfusion range from transfusion-associated circulatory overload, which

*Table* **Price indications for commonly used blood products 2012–13** [2]

| Product | Cost per unit |
|---|---|
| Red cells | $345.14 |
| Pooled platelets | $356.62 |
| Fresh frozen plasma | $279.29 |

occurs in approximately 1/100 transfusions, to the very rare but widely feared risk of viral transmission, which has an estimated per-unit risk of less than 1/1 000 000 for HIV.[10]

As with any biologically derived product, blood components have an inherent degree of variability. Although infectious risks have decreased, the non-infectious risks have remained relatively unchanged.

When deciding whether to transfuse, the risks associated with transfusion must be weighed against the expected benefits to the patient, including the risks of not transfusing. Previously under-recognised adverse effects of transfusion are being increasingly reported. These include the increased incidence of postoperative infection, increased length of hospital stay and increased morbidity and mortality in certain circumstances.[11-13] Multiple studies have shown that clinical outcomes of patients treated with a restrictive transfusion strategy are similar to or better than those treated with a more liberal approach to transfusion.[11] However, these studies were performed in specific groups of hospitalised patients, and results may not be directly applicable to all patient groups.

## Blood products

Blood products comprise three broad categories: fresh blood products, plasma products and recombinant products (see Fig.).

### *Fresh components*

These are manufactured by separation of blood into its components by centrifugation.

### *Red cells*

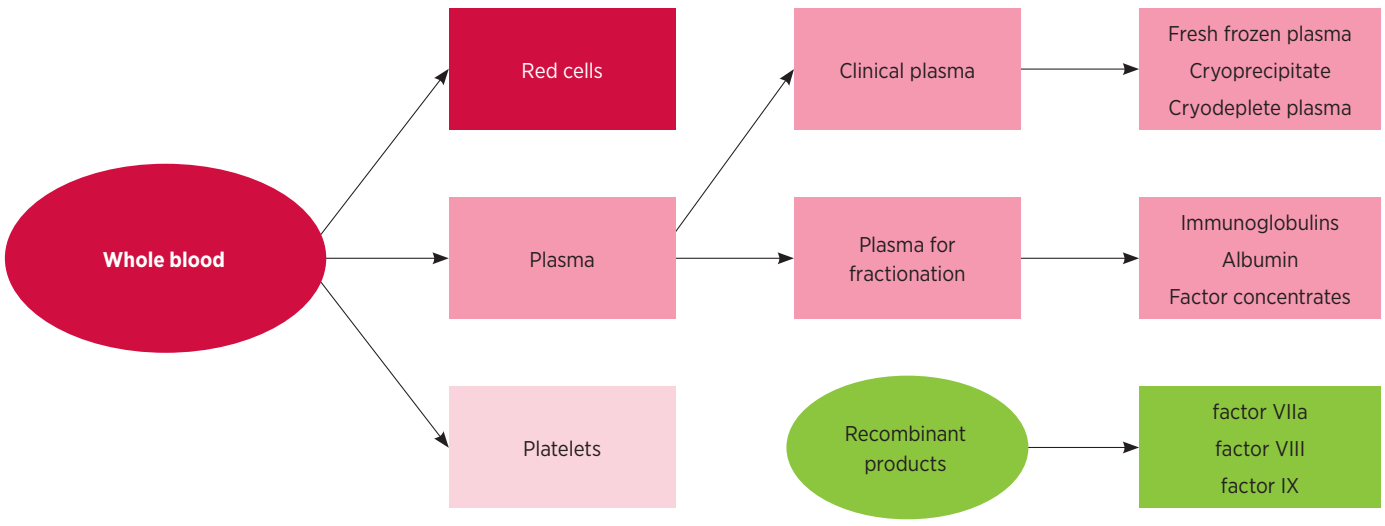
Red cells are used to improve the oxygen-carrying capacity of blood in cases of clinically significant, symptomatic anaemia. A third of red cell transfusions in Australia are used in support of surgery (elective and emergency), a third in haematology and oncology patients, and a third in medical and other contexts.[8]

Faced with the situation whereby both anaemia and its treatment with transfusion are associated with unfavourable outcomes, early and adequate investigation for anaemia is important to identify the underlying cause and consider alternatives to transfusion. This is particularly the case in patients who need elective surgery, as timely identification and treatment of anaemia could obviate the need for transfusion in the perioperative period.

Therapy could include iron supplementation (oral or intravenous) in the case of iron deficiency anaemia. Reticulocyte counts improve in as little as three days and haemoglobin should increase appreciably within two to three weeks. Correction of anaemia and repletion of iron stores can take 3–6 months with oral iron supplements, but can occur more rapidly with intravenous preparations.[14] Less commonly vitamin $B_{12}$ or folate need to be replaced.

Erythropoiesis-stimulating drugs increase haemoglobin concentration in many anaemic patients, but supraphysiological doses are required outside the context of renal failure. However, there is an increase in the risk of thromboembolic disease in the short[15,16] and long term[17] and these drugs have a trophic effect

*Fig.* **Blood and recombinant products**



on some cancers.[18,19] They have limited use outside the approved indication of chronic renal disease.[20]

If transfusion therapy is necessary for anaemia, the aim of red cell transfusion is not to normalise the haemoglobin concentration, but to improve the oxygen-carrying capacity of the blood to tissues. As tissue hypoxia cannot be directly measured, clinical assessment of the patient and evaluation of the pre-transfusion haemoglobin concentration are the primary considerations in the transfusion decision.


When prescribing red cells for transfusion in the patient without active bleeding, a single unit is recommended with clinical reassessment. If necessary, assessment of the haemoglobin increment should guide the need for further transfusion. This single unit policy is not appropriate in actively bleeding patients, those with severe anaemia, or in chronically transfused patients who need ongoing transfusion.

Although there is no haemoglobin concentration below which transfusion is always necessary, levels below 70 g/L are associated with increased mortality.[21] In most situations, transfusion is likely to be appropriate at this point.[22]

### *Platelets*

Platelet transfusions are used in actively bleeding patients with severe thrombocytopenia (generally regarded as platelet counts <50 x $10^9$/L), platelet dysfunction as a result of inherited or acquired abnormalities, and as prophylaxis in severely thrombocytopenic patients at high risk of bleeding. Platelets are also used in cases of massive transfusion.

It is crucial to identify the cause of thrombocytopenia, as platelet transfusion is ineffective in immune-mediated platelet destruction, and may be contraindicated in some thrombocytopenic conditions. The risk of bleeding is also influenced by factors other than platelet count, including infection, concomitant medicines, vascular injury and coagulopathy.

### *Fresh frozen plasma*

Fresh frozen plasma comprises the acellular component of blood and contains all of the coagulation factors. It is used in patients with coagulopathy who are bleeding, or at risk of bleeding, when more specific therapy is not appropriate or available. Fresh frozen plasma is most commonly used in massive transfusion, cardiac bypass, liver disease or acute disseminated intravascular coagulopathy. Abnormalities in coagulation tests such as prothrombin time or activated partial thromboplastin time are poorly predictive of bleeding,[22-24] and prophylactic use to correct laboratory abnormalities is not recommended.

Cryoprecipitate and cryodepleted plasma are derived from fresh frozen plasma. Cryoprecipitate contains most of the factor VIII, factor XIII, von Willebrand factor, and fibrinogen. Cryodepleted plasma contains all the other coagulation factors. These products have limited indications. Cryoprecipitate is used for hypofibrinogenaemia, and cryodepleted plasma is used in plasma exchange for thrombotic thrombocytopenic purpura.

## *Plasma products*

These are fractionated from plasma and are classified into three groups: immunoglobulins, coagulation factor concentrates and albumin preparations. The main indication for these products is to replace reduced or dysfunctional plasma proteins. Immunoglobulin preparations and RhD immunoglobulin are used to elicit an immunomodulatory response.

### *Immunoglobulins*

Immunoglobulins can be divided into two groups – normal immunoglobulin and hyperimmune immunoglobulin.

#### Normal immunoglobulin

This is prepared from normal donors and contains normal concentrations of antibodies against prevalent infections. It is available in intramuscular, intravenous and subcutaneous formulations. These immunoglobulins are used in inherited and acquired immunodeficiency syndromes to replace deficient immunoglobulins. They are also used as an immunomodulator in a range of haematological, neurological, dermatological and inflammatory conditions. Approved indications are detailed in the 'Criteria for the clinical use of intravenous immunoglobulin in Australia'.[25]

Intramuscular preparations are used for passive immunisation of susceptible contacts of patients with infections such as measles, rubella, poliomyelitis and hepatitis A to provide immediate protection against infection. Guidance in specific situations is provided in the Australian Immunisation Handbook.[26]

#### Hyperimmune immunoglobulin

This is prepared from donors who have responded to a specific infection or immunisation and contains high concentrations of specific antibody. These products can be used in the management of exposure to specific infections in susceptible patients.[26]

Exposure to rabies and the Australian bat lyssavirus are treated with rabies hyperimmune globulin. Individuals at high risk of these infections should be actively vaccinated. Rabies immunoglobulin is in short supply and is only available from public health units.[26]

RhD immunoglobulin (anti-D) is used to prevent immunisation of RhD negative women to the RhD antigen and consequently RhD haemolytic disease of the newborn. Current recommendations include a routine antenatal schedule for RhD negative mothers after potentially sensitising events such as miscarriage or the birth of an RhD positive baby. Guidelines on the prophylactic use of RhD immunoglobulin are available from the National Blood Authority.[27]

### *Factor concentrates*

These are indicated for patients with specific factor deficiencies and a haematologist would normally be involved. The main exception is warfarin reversal with prothrombin complex concentrate in patients who are bleeding and have an elevated INR. Consensus guidelines for warfarin reversal have recently been updated.[28] There is currently no evidence to recommend factor concentrates for the treatment of bleeding in patients taking anticoagulants such as dabigatran, rivaroxaban and apixaban.

### *Albumin*

Albumin is available in 4% and 20% formulations. The 4% preparation can be used in the management of shock associated with hypoalbuminaemia, or as exchange fluid in therapeutic plasmapheresis. The 20% preparation can be used to treat critically ill patients with severe hypoalbuminaemia or severe burns.

## Recombinant products

Recombinant products are manufactured from genetically engineered cell lines and are not purified from blood. They are generally coagulation proteins used for inherited bleeding disorders in which there is a deficiency of a specific protein in the coagulation cascade, for example, recombinant factor VIII for haemophilia A and recombinant factor IX for haemophilia B. They may also be used for patients with bleeding disorders who have developed antibodies that interfere with usual therapy. The costs associated with these products are significant, but they are the safest option and are used whenever possible.

## Patient blood management

Patient blood management refers to the management and preservation of the patient's own blood with the aim of reducing or avoiding the requirement for the transfusion of blood components.[29] Evidence-based prescribing of blood products is an essential tenet of this strategy to minimise inappropriate transfusion. The three 'pillars' of patient blood management include:[30,31]

- optimising red cell production
- minimising blood loss
- optimising physiological tolerance of anaemia.

The shift from component-based guidelines emphasises the importance of correlation with the clinical scenario to achieve the best patient outcomes using evidence-based transfusion practice. The National Blood Authority is developing six evidence-based patient blood management guidelines, each focusing on a patient-based clinical approach. The first four modules are available online* and as a free iPad app (BloodDocs, via the App Store). These comprise guidelines for critical bleeding/massive transfusion and perioperative, medical and critical care. Obstetric and paediatric/neonatal modules are currently being developed.

## Conclusion

The increasingly evidence-based application of therapeutic decision making in transfusion medicine has the potential to improve patient outcomes, reduce healthcare costs, and slow the inevitable deficit in supply. In the alignment of economic and therapeutic considerations, there is the opportunity for widespread adoption of patient blood management principles. The evidence-based patient blood management guidelines released by the National Blood Authority provide scenario-specific, patient-based guidance and can be accessed online. <

* www.blood.gov.au/pbm-guidelines

*Rebecca Adams: no conflict of interest declared*

*Robert Bird owns ordinary shares in CSL and is on medical/scientific advisory boards for Amgen and Novartis. He has previously accepted honoraria for speaking at overseas meetings sponsored by Amgen and Novartis, and sponsored travel to overseas conferences from Amgen, GSK, Novartis, Novo Nordisk and Roche.*

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