# Current and Future Alternatives for Allogeneic Blood Product Transfusions

*a report by*

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The transfusion of allogeneic blood products is a complex medical therapy relying on materials that are often available only in short supply and carry a number of substantial risks for the recipient. Perhaps the most feared complication of transfusion is the transmission of infectious diseases. Patients receiving blood products are potentially exposed to any number of micro-organisms, including bacteria, parasites and viruses, despite thorough testing.[1] Less well known, but equally problematic, are the adverse events associated with the infusion of blood products, which include severe lung injury, red blood cell (RBC) haemolysis and anaphylactic reactions.[2,3] Blood transfusion should be reserved for those instances where it is indicated and no other alternatives exist. Furthermore, blood products are often in high demand and shortages in RBCs, platelets and plasma can be problematic even in those cases where transfusion is clinically appropriate.

In some cases, blood transfusion may not be an option even when clinically indicated. Prior to blood product transfusion, the risks and benefits must be explained and patient consent given. Adult patients have the right to refuse blood transfusions altogether for personal or religious reasons. For example, well known for their refusal of all blood transfusions, with the possible exception of factor concentrates, are over 6.7 million practising Jehovah's Witnesses.[4] While the courts are able to offer protection to children in their best interests if parents refuse necessary treatment, transfusion to a non-consenting adult is considered an assault. For such patients, alternatives to blood transfusion are of paramount importance.[5–7]

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As a result of the potentially harmful effects of blood transfusion, the finite supply of blood products and the routine refusal of transfusion by some groups, several alternatives to allogeneic transfusion therapy have been created. In addition, continuous progress has been made in the development of synthetic platelets and oxygen-carrying molecules, as well as recombinant coagulation factor concentrates and human-derived coagulation factor/complex concentrates, which provide maximal therapeutic benefit while substantially eliminating or reducing the risk of transfusion-transmitted diseases. This aim of this article is to review the current status of alternatives to allogeneic transfusions and to highlight new transfusion-related therapies.

## Alternatives to Red Blood Cell Transfusion

The development of synthetic alternatives to RBC transfusion has primarily focused on artificial carriers that are designed to deliver oxygen to peripheral tissues. Currently, there are two broad categories of oxygen carriers: perflurocarbons and haemoglobin-based oxygen carriers (HBOCs).[8,9] In addition to these options, there are several other alternatives to RBC transfusion, which are discussed under the 'Peri-operative Transfusion Alternatives' section of this article.

### *Perflurocarbons*

Perflurocarbons (PFCs) are emulsions suspended in an aqueous medium that absorb and release oxygen by diffusion. PFCs have been used in clinical settings to increase oxygen delivery, particularly during cardiac surgery.[8,9] A significant drawback for PFCs is an inability to deliver large quantities of oxygen. At best, oxygen delivery capacity approaches 30% of normal human whole blood. PFCs also have relatively long half-lives, with excretion occurring over weeks to months after exposure.[8,9] Additionally, the administration of these synthetic carriers can result in myalgias, fever and transient thrombocytopenia.[8,9] Although recent developments, such as a PFC formulation consisting of microbubbles that can increase oxygen delivery capacity to nearly 50% of that of whole blood, improvements are necessary before PFCs can be considered a blood substitute in the future.[8,9]

### *Haemoglobin-based Oxygen Carriers*

An HBOC is a purified haemoglobin compound stripped of its red cell stroma and reduced to the fundamental oxygen-carrying component. HBOCs are designed to increase oxygen-carrying capacity while reducing the risks commonly associated with allogeneic RBC transfusion. Significant problems encountered in previous formulations of HBOCs were recipient renal dysfunction, nausea and vomiting.[8,9] Recipient vasoconstriction, due to nitric oxide scavenging by free haemoglobin, was another problem encountered with initial HBOC products.[8,9] First-generation HBOC use was also limited by the short circulating half-lives of these molecules. As such, current approaches in HBOC engineering have focused on modification of the haemoglobin molecule to increase

circulating half-life while simultaneously decreasing the affinity of oxygen for free haemoglobin, which is higher than that of haemoglobin when bound to RBC stroma.[8,9] Improvements made to HBOCs have included haemoglobin polymerisation involving the cross-linking of stable haemoglobins, conjugation of haemoglobin to larger molecules and encapsulation of haemoglobin within a phospholipid or polymer vesicle.[8,9] These modifications have led to improved tolerance of HBOC administration with decreased recipient side effects.[9] However, even modified HBOCs are rapidly cleared by the immune system, resulting in a half-life of approximately 24 hours.[8,9] Recipient vasoconstriction also remains a concern.[9] Currently, several examples of newer-generation bovine- and human-derived HBOCs – including Hemopure® (bovine), Hemospan® (human) and Polyheme® (human) – are undergoing clinical trials to determine their efficacy and safety profile.[9]

## Alternatives to Plasma Transfusion

### *Recombinant Coagulation Factor Concentrates*

The development and clinical use of recombinant coagulation factor concentrates revolutionised the care of patients with haemophilia. Before the late 1980s, coagulation factor replacement was provided by pooling plasma/cryoprecipitate from a large number of donors.[10] As this era had yet to see the development of highly sensitive nucleic-acid-based testing and rigorous donor screening, a large number of patients with haemophilia A and B were unwittingly exposed to viruses such as HIV, hepatitis B and C and human T-cell leukaemia virus (HTLV).[10]

As biotechnological advances allowed for the creation of recombinant protein products, these techniques were applied to clinical haematology to yield recombinant coagulation factors.[10] These highly purified, lypholised, virus-free coagulation factors are derived from transfected mammalian cell cultures (e.g. Chinese hamster ovary lines).[8,10] Currently, there are several commercial variants of recombinant factor VIII and factor IX used for patients with moderate to severe haemophilia A and B.[11] In addition to these therapies, other recombinant coagulation factors have been produced. Perhaps the best known and most widely used of these agents is recombinant factor VIIa. This recombinant factor has become a first-line agent for the treatment of severe haemorrhage and bleeding prevention in patients with congenital factor VII deficiency, or as a bypass agent in patients with haemophilia A or B who have acquired inhibitors (antibodies) to factor concentrates.[12–15] Recombinant factor VIIa has also been utilised in a number of other clinical trials for patients with massive trauma and intracranial bleeds and those undergoing hepatobiliary or spinal surgery.[16–19] The use of factor VIIa in these situations is a hotly debated matter, as many clinical trials show a significant reduction in allogeneic transfusions but statistically little significant improvement in patient mortality.[20,21] A greater number of randomised trials, rather than anecdotal case reports, are necessary to better determine the appropriate doses and therapeutic efficacy of recombinant factor VIIa for the prevention and treatment of haemorrhage in patients without haemophilia.

With the use of non-protein stabilisers, the viral transmission risks of recombinant factor concentrates are virtually eliminated. Despite this, recombinant factor concentrates are not without their own share of problems. As mentioned above, chronic dosing of factor VIII or IX for patients with severe haemophilia can lead to the development of antibodies, or inhibitors, against coagulation factors, thereby limiting their therapeutic utility.[12] Recombinant factor VIIa – a potent activator of the coagulation cascade – has caused severe and even fatal thromboembolic episodes, particularly in individuals with underlying cardiac or veno-occlusive diseases.[22] In addition to safety concerns, the price of recombinant factor concentrates can be prohibitive as doses for adult patients weighing 50–70kg can cost US$4,000–6,000 per administration.[23]

### *Human-derived Factor/Factor Complex Concentrates*

In addition to the increasing variety of recombinant coagulation factors available for therapy, several human-derived factor/factor complex concentrates are still in use. Humate-P® and Alphanate® are factor complexes consisting of von Willebrand factor and factor VIII used mainly for treatment or prevention of bleeding in patients with von Willebrand disease. Prothrombin complex concentrates consist of vitamin-K-dependent factors (II, VII, IX and X) and include complexes such as Bebulin® and Profilnine®. Another variant of the prothrombin complex concentrate is factor VIII inhibitor bypassing activity (FEIBA), which contains activated factor VII in addition to factors II, IX and X. These activated factor complexes are alternative treatment modalities for patients with haemophilia who have developed inhibitors to factor concentrates.[24,25] There is also a growing body of literature demonstrating the utility of prothrombin complex concentrates for the reversal of coagulopathic states in patients on vitamin K antagonists who cannot tolerate large volumes of fresh frozen plasma (FFP).[26,27]

In addition to human-derived factor complexes, a number of human-derived factor concentrates are available for clinical use. Most of these products are purified with monoclonal antibodies and include agents such as Mononine® (factor IX replacement) and Monoclate-P® (factor VIII replacement), used for treatment of haemophilia.

Unlike recombinant coagulation factors, human-derived factor/complex concentrates carry the potential for transmission of infectious diseases. However, most are manufactured using virus-inactivation techniques, in addition to vigorous donor screening and testing. Although human-derived factor therapies are less expensive than recombinant factor concentrates, they are still costly.[23]

### *Vitamin K Supplementation*

For patients who are vitamin-K-deficient or for those taking vitamin K antagonists such as warfarin, vitamin K supplementation should be considered a primary therapy for reversal of coagulopathy. According to the American College of Chest Physicians (ACCP), plasma infusion should be used sparingly for patients with vitamin-K-based coagulopathies.[28] According to the ACCP guidelines, oral or intravenous vitamin K is the treatment of choice for most patients with prolonged international normalised ratios (INRs). The use of FFP or plasma substitutes is suggested only for patients with severe or life-threatening bleeding, in combination with a prolonged INR.[28] Proper planning prior to invasive procedures can also prevent the unnecessary transfusion of plasma. Any patient undergoing elective surgery who is taking a vitamin K antagonist should, in conjunction with their physician, develop a strategy to taper doses prior to their invasive procedure, if clinically feasible.

## Alternatives to Platelet Transfusion

### *Platelet Substitutes*

From the viewpoint of a blood bank or transfusion service, platelets are

the blood products most difficult to maintain without unnecessary wastage. This is not necessarily due to a lack of adequate blood donors, but is rather a consequence of the five-day shelf-life of stored platelets. Unlike other blood products, there are no options for long-term platelet storage such as freezing and refrigeration due to the inevitable incapacitation of platelet function.[29] A role of platelet substitutes would be for use at times of short supplies of platelets. Additionally, platelet substitutes could be helpful for individuals who develop immunological refractoriness to allogeneic platelet products, a common scenario for patients who have undergone multiple transfusions.[30]

Attempts at synthesising novel platelet substitutes have revolved around pro-coagulant modification of human proteins. For instance, one set of animal studies has shown resolution of haemorrhage in thrombocytopenic rabbits infused with fibrinogen-coated albumin particles.[8,31] Other basic science approaches have focused on using semi-synthetic particles coated with platelet receptors to stop acute bleeding episodes.[8] Another option is the use of infusible platelet membranes. These agents – expressing platelet receptors – activate adhesion and aggregation pathways and promote clot formation.[32] While the results of many of these studies are promising, further research needs to be performed before substitutes are available as a viable alternative to allogeneic platelet transfusion.

### *Pro-coagulant and Antifibrinolytic Medical Therapies*

In addition to providing platelet products for the bleeding patient, many attempts have been made to augment the process of fibrinolysis or induce a pro-thrombotic state to slow haemorrhage. Among the most common agents used to prevent or control bleeding for patients with von Willebrand disease is 1-deamino-8-D-arginine vasopressin (DDAVP), a synthetic form of desmopressin that acts to stimulate the release of von Willebrand factor from endothelial cells.[33] DDAVP has also been shown to be useful in the treatment of platelet bleeding associated with uraemia. In this condition, platelet transfusions are generally futile, as allogeneic and endogenous platelets alike are exposed to a toxic milieu. Thus, for uraemic bleeding, not only is DDAVP an alternative to transfusion, but it also represents a better therapeutic modality.[34,35]

Another set of drugs used to stem platelet-related bleeding are antifibrinolytic agents such as aprotonin, epsilon-aminocaproic acid and tranexamic acid.[36] These therapies are commonly employed in the setting of bleeding that is refractory to platelet transfusions.[36] Additionally, aprotonin and, to a lesser extent, tranexamic acid have been shown to reduce the need for allogeneic blood product transfusion in the setting of hepatic, cardiac and orthopaedic surgery.[36,37] These therapies do carry a risk of hypersensitivity reactions after repeated exposures.[36,38] Additionally, the US Food and Drug Administration (FDA) has recently released details about the potential hazards of aprotonin. This drug has been associated with an increased risk of mortality, as shown by a large Canadian study in which antifibrinolytic agents were utilised to reduce allogeneic blood transfusion during surgery.[39] As a result of this study and FDA recommendations, the manufacturer of aprotinin has removed the drug from the US and Canadian marketplace.

## Peri-operative Transfusion Alternatives

### *Intra-operative Cell Salvage*

Intra-operative cell salvage (ICS) is a tool commonly used to reduce transfusion requirements in the operating room, particularly for procedures where anticipated blood loss exceeds 1,000ml.[40] The technique involves the collection of shed blood that is centrifuged and washed of contaminants and debris before re-infusion into the patient. This technique is efficient at reducing allogeneic transfusions in the operative setting.[40] Although objections have been raised about the use of ICS during surgeries for patients with malignancy, there is little evidence to suggest widespread metastasis or worse outcome for these patients, particularly if irradiation is used for salvaged products.[41–44] Despite the success of ICS, there are contraindications to this collection process, including active treatment with thrombotic or thrombolytic agents, surgical site contamination with urine or bowel contents and patients with underlying haemoglobinopathies.[40] While ICS is seemingly safe and has not been correlated with increased post-operative infection risk, salvaged RBCs have been shown to be contaminated with microbes from the surgical environment.[45]

### *Acute Normovolaemic Haemodilution*

In the late 1970s, physicians were seeking to develop alternativee techniques to reduce RBC transfusion intra- and post-operatively. Acute normovolaemic haemodilution (ANH), based on models of the physiology of blood loss during surgery, involves the collection of an autologous whole blood unit immediately prior to initiation of surgery.[46] The volume of whole blood removed is immediately replaced with a colloid or crystalloid solution, leaving patients essentially normovolaemic.[46] Should bleeding occur, the haematocrit of the lost whole blood would be reduced secondary to haemodilution. Additionally, in the face of haemorrhage a fresh, autologous whole blood unit containing RBCs, coagulation factors and platelets is available at the bedside.[46] ANH, although not widely employed, has been shown to reduce allogeneic blood product usage in a multitude of settings, including various cardiac, orthopaedic, oral, maxillofacial and liver surgical procedures.[40,46–48] Patients who qualify for a trial of ANH include those undergoing procedures where blood product infusion is likely, those who possess a pre-operative haematocrit greater than 12mg/dl and those who lack significant underlying diseases or infections.[46]

### *Crystalloid, Colloid and Albumin Volume Replacement*

In the setting of acute haemorrhage secondary to trauma, blood transfusion may not be an ideal first-line therapy, particularly if volume replacement is initially desired.[49] In fact, because of limited supply and risk factors, blood products should never be used for volume replacement alone.[49,50] For the acutely bleeding patient, several alternatives to blood transfusion exist, including crystalloid solutions (e.g. Lactated Ringer's solution, isotonic saline) and colloid formulations such as starch solutions or albumin.[50] Recent meta-analyses have shown that there is no survival advantage in providing colloids or albumin instead of crystalloids; thus, for the patient presenting with acute bleeding, standard crystalloid formulations should suffice in replenishing lost volume.[50]

For the acutely bleeding individual, the decision to initiate RBC transfusion should depend on tissue oxygen consumption, underlying patient disease status and total blood volume loss rather than 'target' haemoglobin and haematocrit.[49] In some studies, conservative transfusion strategies have been shown to lead to better overall patient outcome and survival.[50] Often, a well-designed massive transfusion

protocol crafted with the input of surgical, haematological, critical care and transfusion physicians may itself serve to limit the use of allogeneic blood products.[51,52]

### *Autologous Blood Donation*

In preparation for a major invasive surgical procedure, patients may opt to donate one or more units of autologous whole blood, particularly for those procedures where significant blood loss is expected and/or allogeneic transfusion is probable.[40] Unlike the requisite stringent criteria for donation of an allogeneic RBC unit, many patients may qualify as autologous RBC donors. According to the American Association of Blood Banks (AABB), patients eligible for autologous donation include those with haemoglobin ≥11g/dl or haematocrit ≥33%, those donating more than 72 hours pre-operatively and those without any obvious clinical or laboratory evidence of bacteraemia.[53] Some patients, such as Jehovah's Witnesses, do not accept autologous units as part of their prohibition against receiving blood. In spite of more liberal donation criteria, some patients are not candidates for autologous donation.

Despite a reduction in the risk of blood product incompatibility and transfusion-transmitted diseases, autologous whole blood transfusion is accompanied by its own unique set of drawbacks. Whole blood autologous units can be used only for oxygen-carrying capacity as platelets and coagulation factors reduce function due to the temperature and length of storage of the autologous unit. Thus, patients who develop coagulopathy or thrombocytopenia may require some form of allogeneic transfusion. If surgical procedures are postponed or autologous blood units not utilised, autologous donations are often wasted and can be an inefficient allocation of healthcare resources.[40] Although autologous units do decrease the risk of incompatible transfusions and limit infectious disease exposure, patients receiving autologous units may still be exposed to other risks of transfusion such as septic reactions due to unintentional contamination during unit collection. Febrile transfusion reactions may also occur due to a lack of leukoreduction of autologous whole blood. Finally, autologous units may not provide a reasonable alternative to allogeneic transfusion as recent evidence suggests that those patients who donate autologous units are transfused at higher rates compared with other populations.[54] Future trials must be performed to determine the clinical and cost-efficacy of autologous whole blood donation so that this technique can be applied to populations where it will be of greatest benefit.

A new class of drugs, thrombopoietin-receptor agonists, has shown promising results for the treatment of thrombocytopenia in patients with hepatitis C cirrhosis and immune-mediated platelet destruction.

### *Parenteral and Oral Iron Administration*

The provision of iron is indicated for patients with severe, clinically significant iron-deficiency anaemia. However, there is also evidence to suggest that patients undergoing surgical procedures may benefit from pre-operative oral and/or parenteral iron therapy. In the post-operative state, patients increase expression of cytokines and other chemical markers of inflammation due to systemic stressors.[39,54,55] This prolonged inflammatory state may contribute to the phenomenon of post-operative iron-deficiency anaemia.[55,56] Several trials in plastic, colorectal and orthopaedic surgery have demonstrated that patients provided with pre-operative doses of either parenteral or oral iron had lower allogeneic blood transfusion requirements in the post-operative period.[55,57–60] Interestingly, a trial of post-operative intravenous iron plus an erythropoietin-stimulating agent (ESA), with no pre-operative regimen, showed no benefit in recovery of anaemia.[61] Further studies are needed to determine whether parenteral or oral iron therapy may be of use pre-operatively in other surgical settings.

## Haematopoietic Growth Factors

### *Erythropoietin-stimulating Agents*

For the anaemic or pre-operative patient, a widely used therapeutic strategy includes increasing production of endogenous RBCs with recombinant erythropoietin.[62] The use of ESAs immediately prior to surgery in otherwise healthy patients likely provides clinical benefit and reduces post-operative allogeneic RBC transfusion. However, this strategy is of limited utility without the simultaneous provision of iron by the oral or intravenous route.[40,59,63] ESAs are also commonly used to successfully treat anaemia related to chronic renal disease.[64]

In recent months, the use of ESAs in lieu of RBC transfusion for anaemia associated with malignancy has been heavily scrutinised. The most influential study was a phase III clinical trial performed in patients with non-small-cell carcinoma of the lung, which showed decreased patient survival following chronic ESA administration.[65] As a result of this and other earlier cancer-related anaemia trials showing poor patient outcome with ESA dosing, the FDA issued a 'black box warning' for ESA administration.[66–68] In addition to these findings, trials performed in other anaemic, critically ill patient populations revealed that ESA dosing did not significantly decrease allogeneic RBC transfusion.[69] Furthermore, ESA administration was associated with a significant increase in the incidence of thrombotic events.[69] As more data about the use of ESAs are collected in clinical trials, appropriate patient population selection and criteria are needed in order to guarantee better safety and outcomes with these agents.

### *Platelet- and Leukocyte-stimulating Agents*

A new class of drugs, thrombopoietin-receptor agonists, has shown promising results for the treatment of thrombocytopenia in patients with hepatitis C cirrhosis and immune-mediated platelet destruction.[70–72] These drugs, such as eltrombopag and AMG 531, appear to stimulate megakaryocyte division in the bone marrow, increasing circulating platelet counts.[70–72] Thrombopoietin-receptor agonists might be particularly useful in patient populations who show refractoriness to platelet transfusion. Further studies are currently under way for this exciting new class of drugs. The use of recombinant myeloid colony-stimulating factors (CSF) such as granulocyte-CSF has also improved care of patients with severe leukopenia, allowing for increased production of endogenous myeloid cells.[73]

## Summary

There are many excellent, reliable and safe alternatives to transfusion

that have been embraced by surgeons, anaesthesiologists, haematologists and intensive care physicians. These therapies provide maximal clinical benefit with few of the risks associated with allogeneic transfusion. In the coming years, additional advances should arise to further complement current strategies. While these treatment modalities are unlikely to supplant allogeneic blood products, their use will greatly aid transfusion services in providing safe and effective patient care. ■


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