

# Strategies to reduce allogeneic blood transfusion

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## Abstract

*Blood is scarce and there will never be zero risk. Thus, multidisciplinary approaches to reduce or avoid allogeneic blood transfusion in medicine and surgery are discussed.*

*In medical patients — depending on the situation — causes of anaemia should be investigated, nutritional deficiencies corrected and erythropoietic stimulating agents (ESA) used with or without intravenous (iv) iron.*

*In surgical patients, it is important to check the blood count, evaluate the history of bleeding and drug therapy far in advance of surgery to allow time for diagnosis, anemia correction, haemostasis optimization or decision for a pre-deposit autologous donation.*

*During intraoperative period bleeding can be minimized through the use of anaesthetic and surgical techniques, correcting hypothermia, acidosis, hypocalcaemia or hyperkalemia. Also the use of pharmacological agents such as haemostatic sealants, antifibrinolytics, procoagulants and methods of autologous transfusion (acute normovolemic haemodilution, intracellular cell salvage) helps minimize the dependence on allogeneic blood transfusion. During acute bleeding, the use of thromboelastometry gives a full haemostasis overview and allows for more targeted use of platelet concentrates and fibrinogen. It has also been shown to reduce intraoperative transfusion requirements in high-risk surgical patients.*

*In conclusion, the above-mentioned strategies, when included in protocols and guidelines, can substantially contribute to the reduction of the use of allogeneic blood.*

**Key words:** allogeneic, erythropoietic stimulating agents, haemostasis, autologous blood, thromboelastometry

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## Introduction

Strategies to minimize or avoid allogeneic blood transfusion must always be taken into consideration. Blood is scarce, expensive and there will never be zero risk. That is why benefits and risks must be carefully weighted for each individual patient.

Blood remains essential for many bleeding surgeries, such as cardiac, liver, trauma or other surgical procedures or for patients with malignancies who cannot be given chemotherapy without the support of blood components [1]. The use of

erythropoietic stimulating agents, the management of nutritional deficiencies, the administration of pharmacological agents to support hemostasis, as well as well-defined policies for surgical patients may limit the use of allogeneic blood. And for this purpose protocols and guidelines are required.

## Reasons for minimization and avoidance of the use of allogeneic blood

Although many advances have been made in the procedures that help to avoid transfusion-transmitted infections, zero risk does not exist [2].

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**Table 1.** Reasons to avoid/minimize allogeneic blood

<b>Residual risks of transfusion-transmitted infections</b>
Window period'
Not screened
Unknown
Emergents
<b>Transfusion reactions</b>
Immune
Non-immune
<b>Highcost</b>
Universal leukocyte reduction
Nucleic acid amplification technology
Microbial inactivation procedures
<b>Blood is scarce</b>
Old donors
Process of blood donor selection
<b>Rejection of blood transfusion</b>

There are many factors that need to be considered such as donors in the 'window period' of infectious diseases, not screened agents, emerging agents (WNV, malaria, *Trypanosoma cruzi*), unknown viruses, new agents that seem to appear every 5 years or so, as well as transfusion immune or non-immune reactions. Shortage of blood may also result from regular donors getting older or from donors being unsuitable due to their higher-risk life styles (body piercing, tattooing, international travel, etc.). Moreover, the cost of blood is rising due to the use of new screening technologies, universal leukocyte reduction, pathogen inactivation and irradiation of some blood components. Finally, allogeneic blood is forbidden in Jehovah's Witness patients because of their specific interpretation of the Scriptures (Table 1).

### Transfusion in medical patients

Red blood cell (RBC) transfusions are administered to patients to improve oxygen supply to the tissues. Rapid increase in hemoglobin (Hb) levels is achieved but the benefits are transient. Such transfusions are used for symptomatic patients and/or those who need rapid improvement of Hb. Prophylactic transfusion is not recommended.

The WHO defines anemia as Hb < 13 g/dl in ♂ and Hb < 12 g/dl in ♀. Any level of anaemia should be investigated and treated for its underlying cause (s). The most common anemias are due to nutritional deficiencies (iron, vitamin B12, foliates).

**Table 2.** Indications for iv iron

— Per os iron intolerance
— Malabsorption (celiac disease, inflammatory bowel disease, gastric by-pass)
— Ongoing blood loss (e.g. Osler-Weber-Rendu)
— Severe iron deficiency
— Functional iron deficiency (anaemia of renal failure or chronic disease, stimulation of Hb synthesis with ESA)
— Autologous blood donation
— Rapid pre-surgery correction
— Increased iron needs (pregnancy*)

\*Forbidden during first trimester

Iron deficiency, with or without anaemia symptoms, should be treated with iron supplementation to correct the anemia and/or replenish the body stores [3]. Under normal circumstances oral iron is the treatment of choice as it is the most physiological, simple, safe and cheap form but iron can also be administered intravenously for several other reasons (Table 2) [4, 5]

On the other hand it should be kept in mind that iron is a pro-oxidant and as such it is an important source of nutrition for many bacteria. It is therefore contraindicated during acute infections [6].

### Avoiding blood transfusion in cancer patients

In ambulatory cancer patients anemia is determined through ordering at first visit of complete blood count with reticulocytes, measurement of iron parameters [serum iron, total iron-binding capacity, transferrin saturation (Tsat), serum ferritin], vitamin B12, foliates, creatinine and C-Reactive Protein [7].

Anaemia in cancer patients is multifactorial (Table 3), although the most likely causes are anemia of chronic disease (ACD) (Table 4) and chemotherapy-induced anaemia (CIA) [7, 8]. Anemia of chronic disease is mediated by several inflammatory cytokines [7, 9]. IL-6 induces the synthesis of Heparin, a peptid hormone that regulates the efflux of cellular iron and its distribution in the body. It degrades Ferroportin, the main exporter of iron from cells, reducing the accessibility of storage iron from reticulo-endothelial system (RES), as well as iron export from enterocytes to the duodenum. This provokes functional iron deficiency (FID) characterized by the presence of adequate iron stores but insufficient iron available

**Table 3.** Causes of anaemia in cancer patients

Anaemia of chronic disease (ACD)
Myelotoxicity from chemotherapy
Haemolysis
Nutritional deficiencies
Blood loss
Bone marrow infiltration

**Table 4.** Physiopathology of anaemia of chronic disease

Iron absorption/movement restricted in gut and RES
Decrease RBC survival
Inadequate erythropoietin response
Inhibition of differentiation/proliferation of erythroid progenitor cells
Inhibition of erythropoietin production
Decreased erythropoietin levels

for erythroblast production. The same occurs when iron demands are increased by bone marrow stimulation like in therapy with erythropoietic stimulating agents (ESA) [10].

### Erythropoietic stimulating agents

Erythropoietin is a recombinant glycoprotein that contains human-identical amino-acid sequence and is biologically indistinguishable from human erythropoietin. Darbepoietin  $\alpha$  activates the same receptors as recombinant epoetin, but has a two to three times longer half-life due to its higher carbohydrate content, which creates the potential for prolongation of dosing intervals (Figure 1) [11, 12].

The commonly used ESAs include Epoetin  $\alpha$  (40 000 UI), Epoetin  $\beta$  (30 000 UI) given weekly, and Darbepoietin given either 150 mcg weekly, or 300 mcg every two weeks followed by 500 mcg every three weeks.

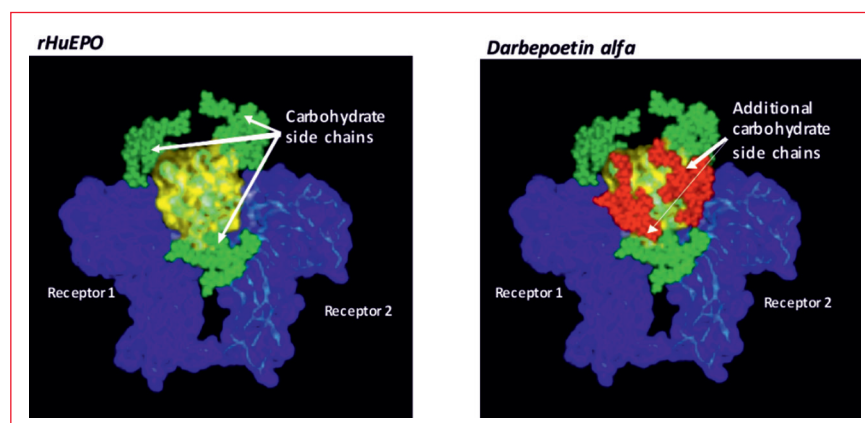
In cancer patients the treatment with ESA of symptomatic chemotherapy-induced anaemia is aimed at improvement of the quality of life and minimization of transfusion requirements. ESA provides a smooth and sustained increase in Hb; it is generally well tolerated and easy to administrate [10].

Blood transfusion however is required for symptomatic patients who need a rapid improvement of Hb, for non-responders to ESA or if Hb < 9 g/dl [7].

Before ESA administration we need to exclude nutritional deficiencies (iron, vit. B12, foliates), blood loss and history of cardiovascular or thromboembolic adverse events. It is also advisable to assess the iron status by measuring Tsat and ferritin. Since iron will be consumed during ESA therapy, periodic monitoring of iron parameters must be performed [10]. Intravenous iron supplementation is required for patients with FID (ferritin  $\leq$  800 ng/ml, Tsat < 20%) or absolute iron deficiency (ferritin < 30 ng/ml, Tsat < 15%) [7].

Iron supplementation improves ESA response in the iron-replete patients. The increment in hemoglobin level is more effective and rapid for patients supplemented with intravenous iron which allows for lower ESA dosage [11, 13]. In ACD patients oral iron is poorly absorbed, so intravenous iron administration is the treatment of choice.

If the hemoglobin level approaches or exceeds 11g/dl, reduction or interruption of the ESA dosage should be considered [11]. ESA should be discontinued following the completion of chemotherapy.



**Figure 1.** Epoetin vs. darbepoietin structure

However, it must be noted that approximately 1/3 of patients under ESA treatment are non-responders. ESA should be discontinued if no 1 g/dl increment of Hb level is reported after 4 weeks of treatment or there is no response over a 12-week escalation period. Such move is indicated to avoid unnecessary long-term therapy or occurrence of adverse events [7, 10].

### **Treatment guidelines**

1. ESA is administered in the management of chemotherapy-induced-anaemia but not anaemia caused by cancer.
2. Prophylactic ESA administration is not recommended.
3. At Hb  $\leq$  9 g/dl transfusion should be considered prior to ESA treatment.
4. Erythropoietin therapy should be initiated when the patient is symptomatic with Hb level 9–10 g/dl.
5. Hb level of  $\leq$  12 g/dl should be the target otherwise there is the risk of thromboembolic events or tumor growth.
6. Individualized treatment should be continued for as long as the patient is on chemotherapy and symptomatic improvement is reported.

### **Transfusion in surgical patients**

#### **Preoperative period**

Preoperative planning is essential for reduction or avoidance of allogeneic blood transfusions. The strategies to avoid allogeneic blood transfusion in surgical patients include correction of pre-existing anaemia, identification and control of coagulation disorders, use of methods for reduction of blood loss and autologous transfusion [14]. They usually involve:

- diagnosis and treatment of nutritional deficiencies (iron, vitamin B12, foliates); optimization of haemostasis;
- erythropoietin and/or intravenous iron administration;
- predeposit autologous donation (PAD).

Three to four weeks before surgery, personal and/or family history of bleeding and anaemia should be evaluated [14]. It is recommended to undertake drug therapy including antithrombotic medication and to make decisions for discontinuation (if safe) or, substitution of agents that could affect clotting during surgery [5, 16, 17].

The following tests need to be performed to identify and timely treat any type of anaemia or bleeding disorder: full blood count, prothrombin

time (PT) and activated partial thromboplastin time (APTT) [16].

Patients with inherited platelet disorders (Bernard-Soulier disease, Fanconi anaemia, Glanzmann's thrombasthenia), or coagulation factor deficiencies (von Willebrand disease, factor II, V, VII, VIII, IX, XI, XII, XIII deficiencies) should be followed in specialized centers and prepared with deficiency factor replacement before, during and after surgery [5, 13]. If the level of anaemia is severe and surgery cannot be postponed, the use of ESA and/or intravenous iron supplementation may be considered to increase red cell mass. This is particularly true for patients with anaemia caused by either renal failure or chronic disease [5]. Also its use can be an option before predeposit autologous donation (PAD) in anaemic patients.

Predeposit autologous donation means collection of the patient's own blood for reinfusion. The use of PAD is considered for surgical patients where blood loss is expected. PAD is collected and stored during the weeks prior to elective surgery. PAD reduces the risk of transfusion-transmitted infections, alloimmunization or graft-versus-host disease. It also provides compatible blood for patients with complex red cell antibodies or antibodies to common red cell antigens. It does not however eliminate the risk of bacterial contamination, ABO mismatch due to clerical errors, some febrile reactions or fluid overload [18].

#### **Intraoperative period**

The combination of several intraoperative strategies enables the performance of major surgery procedures with no need for the use of allogeneic blood components. The following factors may largely contribute to the improvement of hemostasis during surgery:

- choice of anaesthetic and surgical techniques to reduce bleeding;
- patient positioning/hypotension;
- correction of hypothermia, acidosis, hypocalcemia, hyperkalemia;
- restrictive *vs.* liberal transfusion (Hb  $<$  7 g/dl *vs.* Hb  $<$  9 g/dl);
- thromboelastometry;
- pharmacological agents: haemostatic sealants, antifibrinolytics (tranexamic acid,  $\epsilon$ -aminocaproic acid), procoagulants [1-deamino-8-D-arginine vasopressin (DDAVP), fibrinogen, prothrombin complex concentrate, rFVIIa];
- autologous transfusion (intraoperative cell salvage, acute normovolemic haemodilution).



**Figure 2.** Rotem® Delta

Anesthesia choices and positioning for surgery can influence surgical blood loss. Hypothermia (temp.  $< 35^{\circ}\text{C}$ ) is thought to inhibit blood coagulation and impair platelet functions [19]. It is also important to maintain  $\text{PH} > 7.2$ ,  $\text{Ca}^{++}$  serum concentration  $> 1 \text{ mmol/l}$ .

Research studies have also demonstrated that restrictive strategy for red blood cell transfusion is at least as effective as a liberal transfusion strategy in critically ill patients [20].

### Thromboelastometry (Rotem® System) (Figure 2)

Coagulation tests (TP, APTT) and platelet count are of limited help in severe bleeding, as they neither provide enough information in terms of clot formation nor contribute to recognition of fibrinolysis. It also takes too long to obtain the results. Thromboelastometry is a point-of-care coagulation (POC) method for hemostasis testing in whole blood. It permits rapid assessment of the three aspects of coagulation: clot strength, thrombin generation and clot stability as well as a goal-directed coagulation management in emergency situations. It is the gold standard for diagnosis of premature dissolution of the clot (hyperfibrinolysis). Since the method of thromboelastometry was introduced for hemostasis testing a substantial reduction in RBC has been reported and the method serves as a guide to intraoperative transfusion in cardiac, vascular and other bleeding surgeries (Table 5) [16, 21].

**Table 5.** Thromboelastometry characteristics

Uses small quantity of citrated whole blood
Gives full haemostasis overview in 10–15 minutes
Gives clot firmness
Provides more targeted use of platelet concentrates and fibrinogen
Permits diagnosis or exclusion of hyperfibrinolysis
Predicts status of coagulation after protamin

Pharmacologic haemostatic agents should be used when bleeding is wide spread and generalized or when the bleeding site is not accessible. Topical sealants can be used depending on the site and amount of bleeding [20, 22].

The use of rFVIIa in surgical bleeding, although off label, may be effective in bleeding patients who are unresponsive to standard therapy, i.e. with fresh frozen plasma, platelets, fibrinogen [23].

Intraoperative cell salvage refers to the collection and reinfusion of red cells that were lost during surgery. This procedure is performed by machines commonly known as a “cell savers”, which suction, wash the red cells by centrifugation and resuspend them in saline so that blood can be given back to the patient’s body instead of being thrown away. Intraoperative cell salvage is used when the expected blood loss is large ( $> 1,5 \text{ L}$ ) and it is worth noting that the procedure is acceptable also by patients with religious objections to receiving blood such as Jehovah’s Witnesses provided that the collected blood remains in continuity with the patient via tubing connected to the patient’s intravenous cannula and hence, the patient’s circulatory system. Contraindications are the possible aspiration of malignant cells, or the presence of infection, ascitic or amniotic fluids and topical clotting agents [18].

Acute normovolemic haemodilution (ANH) is a method of autologous transfusion that consists in removal of the whole blood before or during induction of anaesthesia, and simultaneous replacement with crystalloid or colloid. If necessary, the blood that was removed is returned to the patient. The major benefit is the reduction of RBC cell losses when whole blood is shed perioperatively at lower hematocrit levels after ANH procedure is performed. The drop in red cells mass contributes to the decrease in blood viscosity and improvement in tissue perfusion. This method should only be considered when the estimated blood loss exceeds 20% of blood volume and the patient does not have a severe myocardial disease [18].

## Postoperative period

Anaemia is common after surgery and is associated with worse outcomes. Strategies to limit the development of anaemia must therefore be adopted. Examples of such strategies are:

- postoperative cell salvage;
- ESA and/or iv iron.

In the postoperative cell salvage procedure, blood is collected from surgical drains, and then reinfused through a special device. The blood is diluted, partially haemolysed and defibrinated and may contain high levels of cytokines [18]. We have no experience with this procedure at Santa Maria Hospital in Lisbon.

Administration of ESA and/or iv iron in the post-operative period contributes to the improvement of Hb levels. Increase of inhaled oxygen content, maintenance of adequate intravascular volume and optimization of cardiac performance augments oxygen delivery. Furthermore, control of fever or shivering and provision of substantial bed rest, may reduce oxygen consumption during the post-operative period.

## Conclusions

It is strongly recommended to adopt strategies which help limit blood loss as well as to develop alternatives to allogeneic blood use in medical and surgical patients. Protocols to guide transfusion decisions are equally important for minimalization of allogeneic blood use. Conventional practices should be based on the needs and expected benefits for individual patients. If all these strategies are adopted, no elective surgeries need to be cancelled for lack of blood and treatment of patients under chemotherapy can proceed with no interruption even if blood shortage occurs.

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