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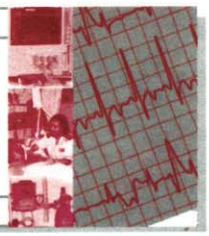
Anaemia and blood transfusion in the ICU



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During the early part of the 20th century blood transfusion became a mainstay of clinical practice. The benefit of blood transfusion in surgery, as well as in other clinical settings, was assumed, and blood transfusion was viewed as relatively risk free. Many advances in the treatment of patients especially in the field of surgery would have been impossible without the availability of blood products.

A dramatic change in thinking occurred in the early 1980s, mainly because of concerns of transfusion-related infection, particularly the human immunodeficiency virus. Although advances in transfusion medicine have greatly decreased the risk of viral transmission from blood transfusion, other issues related to the safety and efficacy of blood transfusion have led to a re-evaluation of transfusion practices. Among the most important of these issues is the transfusion trigger at which the benefits of transfusion outweigh the risks associated with administration of blood products.

Anaemia is a common finding in patients admitted to the intensive care unit, 30% of whom have a haemoglobin of <10.0 g/dl, and 85% of whom require transfusions if they spend more than a week in ICU.[1]

Blood is a scarce and expensive resource in South Africa and attempts should always be made to limit usage and evidence-based guidelines should be followed whenever possible. While optimal blood transfusion practice and transfusion triggers remain controversial, the best practice has yet to be identified. Indications for transfusion continue to be inconsistent among health care providers.

This review focuses on current issues related to transfusion practice, with particular attention given to transfusion triggers in critical care.

Causes of anaemia in the Intensive care unit (ICU)

Anaemia appears rapidly in patients admitted to the ICU. By day 3 after admission 95% of patients are anaemic.[2] Anaemia in critical illness resembles anaemia of chronic disease. The aetiology appears to be multifactoral and involves both decreased production and increased loss of red blood cells (Table I).

Table I. Common causes of anaemia in the ICU

Increased loss	Decreased production
Phlebotomy	Impaired erythropoietin response
Increased destruction	Nutritional deficiencies
Hypersplenism	Bone marrow suppression
Haemolysis	Alterations in iron metabolism
Gastrointestinal bleeding	

Both erythropoietin production and response in critical illness are severely diminished. The mechanisms responsible are poorly understood but are thought to include a cytokine-induced reduction in the expression of erythropoietin genes. Iron metabolism is also severely altered by critical illness. Pro-inflammatory cytokines decrease serum iron concentrations and increase iron storage by the reticulo-endothelial system. This limits the amount of free iron available for erythropoiesis. Low concentrations of vitamin B_{12}, folic acid and iron secondary to impaired nutrition in the ICU may also contribute to anaemia.[3] Phlebotomy is also a significant source of blood loss in the ICU. A recent study[4] reported an average daily blood loss of 41 ml in patients in the ICU. Structural and functional changes that occur in red blood cells in critical illness result in early clearing from the circulation and a decreased lifespan of the erythrocyte. Hypersplenism secondary to chronic illness and haemolysis may also contribute to premature red cell destruction.

Oxygen delivery

Single-celled organisms obtain their oxygen through simple diffusion, a process that is proportional to the difference in partial pressure and the area of the membrane, and inversely proportional to the distance the gas must travel. As these single-cell organisms evolved into multicellular forms and their body plans became more complex, there was a need to overcome the time-distance constraints of diffusion. The red blood cell, respiratory and cardiovascular systems

evolved to provide delivery of oxygen to the various tissues of the body. There are four critical steps in the chain of oxygen transport: *(i)* bulk flow from the atmosphere to the highly vascularised surface of the lung; *(ii)* diffusion into the blood; *(iii)* bulk flow to the various tissues of the body; and *(iv)* diffusion into the mitochondria of each cell.[5]

As oxygen is poorly soluble in water and plasma the respiratory pigment haemoglobin evolved to improve the carriage of oxygen in the blood (Table II).

Table II.	Oxygen carriage in the blood
The oxygen content of blood is calculated by adding the dissolved oxygen to the oxygen bound to haemoglobin Dissolved oxygen (ml/dl) is calculated by multiplying the partial pressure of oxygen with the solubility coefficient of oxygen in blood (0.023 if measured in kilopascals) Oxygen bound to haemoglobin (ml/dl) is calculated by multiplying the haemoglobin concentration with the arterial oxygen saturation. This is then multiplied by 1.39 (the amount of oxygen that binds to one gram of pure haemoglobin)	

The role of haemoglobin as an oxygen carrier can be appreciated by calculating the oxygen content of blood with and without haemoglobin (Table III).

Table III.	Oxygen content of blood using typical values
Oxygen dissolved in plasma	(0.023) (13.3 Kpa) = 0.3 ml/100 ml
Oxygen bound to haemoglobin	(15 g/dl) (100/100) (1.39) = 20.85 ml/100 ml

Using typical values at sea level (PaO_2 of 13.3; oxygen saturation of 100%; haemoglobin 15 g/dl), the role of haemoglobin as an oxygen carrier can be appreciated by calculating the oxygen content of blood with and without haemoglobin (Table III).

Without haemoglobin very little oxygen would be carried in the blood, severely limiting the bulk flow of oxygen to the tissues.

Oxygen delivery is determined by cardiac output and blood oxygen content (Table IV). Oxygen consumption of the tissues is determined both by the oxygen delivery and extent of oxygen extraction.

Table IV.	Oxygen delivery
Oxygen delivery = (cardiac output)(arterial oxygen content) $DO_2=CO \times CaO_2$ Oxygen consumption = (cardiac output) (arterial oxygen content – mixed venous oxygen content) $VO_2 = CO (Ca0_2–CvO_2)$	

In healthy subjects, resting oxygen delivery (DO_2) is approximately 1 000 ml/min, and approximately 250 ml/min of this oxygen is required by tissue metabolic processes (VO_2), so that the usual oxygen extraction ratio is approximately 25%. If oxygen delivery decreases, oxygen extraction by the tissues increases so that oxygen consumption remains relatively constant.

Physiology of anaemia

Anaemia inevitably leads to a reduction in oxygen-carrying capacity of the blood. The physiological response to anaemia involves several compensatory mechanisms to increase oxygen delivery to the body. Compensatory mechanisms are extremely effective in healthy subjects, a haemoglobin as low as 3 g/dl - 5 g/dl can be tolerated without significant organ dysfunction.

Anaemia triggers a number of adaptive mechanisms that attempt to maintain DO_2 even at low haemoglobin levels.[6] Anaemia results in increased cardiac output due to reduced blood viscosity and increased sympathetic outflow. Lowering of viscosity as haematocrit falls may also result in fewer inflammatory interactions between activated platelets and the endothelium. Selective vasoconstriction promotes blood flow to critical organs, whereas oxygen-deprived tissue cells undergo specific hypoxia-induced adaptations. Through increased production of 2,3-diphosphoglycerate in red blood cells, anaemia results in a shift of the oxyhaemoglobin dissociation curve to the right, thereby facilitating oxygen unloading at tissue level.

A critical threshold of oxygen delivery exists at approximately 4.5 ml/kg/min. Below this level oxygen extraction no longer compensates for the delivery deficit and oxygen consumption begins to decrease. From this point, any reduction in oxygen delivery is associated with a decrease in oxygen consumption. A state of supply dependency is said to exist.[7] This threshold of oxygen delivery impairment is thought to correspond with progressive impairment of cellular function.

The myocardium appears to be the organ most

vulnerable to anaemia. Basal oxygen extraction is higher in the myocardium than any other tissue – normally 60% and up to 80% with stress. With high demand, any increase in extraction is almost impossible and the myocardial oxygen supply becomes dependent on coronary blood flow. Patients with ischaemic heart disease are at particular risk.

The critically ill patient is also at significant risk of the adverse effects of anaemia.

Cardiovascular, respiratory and metabolic compromise coupled with a hypermetabolic state may lead to significant oxygen debt and consequent organ dysfunction.

Red cell transfusion as a treatment for anaemia

The most significant risk associated with anaemia is thought to result from the decrease in oxygen delivery. This risk will naturally vary from patient to patient depending on their ability to compensate for the anaemia. It is assumed that anaemia will be poorly tolerated in patients with severe cardio-respiratory disease, the elderly and the critically ill. There are however, few data to support this assumption.

In a retrospective study examining 1 958 patients who refused blood transfusion, Carson *et al.*[8] demonstrated an increase in 30-day postoperative mortality, from 1.3% in patients with a preoperative haemoglobin of ≥ 12.0 g/dl to 33.3% in patients with a preoperative haemoglobin of < 6.0 g/dl.[8] Not surprisingly, patients with documented ischaemic heart disease had a higher risk of death. In a subsequent retrospective cohort study of 300 Jehovah's Witnesses who declined transfusion and had haemoglobin levels of < 8.0 g/dl, the 30-day postoperative mortality was 2.5 times higher for each 1.0 g/dl decrease in haemoglobin.[9] These two studies indicate that a normal preoperative haemoglobin is associated with better outcome, and that the anaemic patient is at higher risk of mortality. Neither study addresses outcome after transfusion.

Several large studies have shown benefits of blood transfusion in the ICU. A combined retrospective and prospective cohort study analysed 4 470 critically ill patients admitted to six Canadian ICUs. In patients with cardiac diagnoses (ischaemic heart disease, cardiac arrest, arrhythmia, and cardiac and vascular surgical procedures), there was a non-statistically significant trend toward increased mortality when haemoglobin concentrations were < 9.5 g/dl.[10] Furthermore, analysis of a subgroup of 202 patients with anaemia, an Acute Physiology and Chronic Health Evaluation (APACHE) II score of > 20, and a cardiac diagnosis revealed that transfusion of between one and three units, or four and six units of red blood cells was associated with a significantly lower mortality rate compared with those patients who did not receive a transfusion.

However other studies have not shown a benefit from blood transfusion. Wu *et al.*[11] showed that transfusion was associated with increased 30-day mortality for patients whose admitting haematocrit values were > 36%.

In another study of patients undergoing hip fracture repair, no benefit of transfusion was found on either 30- or 90-day mortality, and haemoglobin concentrations of ≥ 8.0 g/dl were well tolerated.[12]

Evidence-based medicine supports a conservative approach to the use of red blood cells in the ICU. The TRICC (transfusion requirements in critical care) study by Hébert *et al.*[13] provides the best current evidence regarding the efficacy of blood transfusion in critically ill patients. This prospective, randomised, controlled trial compared a liberal transfusion strategy (haemoglobin, 10 - 12 g/dl, with a transfusion trigger of 10 g/dl) to a restrictive transfusion strategy (haemoglobin, 7 - 9 g/dl, with a transfusion trigger of 7 g/dl). Patients in the liberal transfusion group received significantly more red cell transfusions. Lower overall in-hospital mortality was achieved in the restrictive strategy group, although the 30-day mortality rate between groups was not significantly different. However, in those patients who were less ill (APACHE < 20) or younger (< 55 years of age), the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion arm. Therefore, a restrictive strategy is at least equivalent, and in some patients possibly superior, to a more liberal transfusion strategy.

Why blood transfusions are associated with worse clinical outcomes is unclear. A substantial amount of research published since the early 1980s suggests that exposure to leukocytes in transfused blood may trigger an immune response in the recipient leading to an increased risk of infection, earlier recurrence of malignancy, and increased likelihood of mortality.[14] A significant association between the number of blood transfusions and risk of subsequent infection has been reported in patients after trauma, burns, and a variety of surgical procedures, in both elective and emergency settings.[14] In the critically ill, Taylor *et al.*[15] demonstrated an association between blood transfusion and increased nosocomial infection and mortality in the critically ill. These data have in turn led to the hypothesis that leukocytes in stored blood suppress immunity and that leukocyte-reduced blood should be used. However there are still no data either supporting or refuting the utility of leukocyte depletion.

Subsequent to the publication of the TRICC trial, a study published by Rivers and colleagues[16] showed that early goal-directed resuscitation based on a mixed central venous saturation decreased mortality from

46.5% in the control group to 30.5% in the goal-directed therapy group. One of the many interventions in patients with early septic shock, was to increase the haematocrit to > 30% if the central venous saturations fell below 70%. As a consequence of goal-directed therapy, 64% of patients compared with 18.5% of the control group received red blood cell transfusions. There are significant differences in the patient populations studied by Rivers and colleagues and the TRICC trial. The early goal-directed therapy study does highlight the need to individualise transfusion triggers in subpopulations of critically ill patients.

Risks associated with blood transfusion

A wide range of complications and side-effects are associated with blood and blood product transfusion (Table V). These range from relatively minor problems such as febrile reactions to life-threatening complications such as HIV transmission and anaphylactic reactions. Current viral transmission rates are low and becoming lower with the introduction of advanced testing methods such as nucleic acid testing, which have drastically reduced the infectious window period. New storage methods have also led to a decrease in storage-related transfusion complications.

Currently the most serious risks of blood transfusion arise from administrative error, and also include transfusion-related acute lung injury and bacterial contamination. However, constant vigilance is essential as new pathogens and other previously unrecognised risks are identified.

Ex vivo storage of red blood cells causes a number of morphologic and biochemical changes to the cell and storage media. These are collectively referred to as the 'RBC storage lesion'. Blood stored for more than 7 days in acid citrate dextrose is depleted of RBC 2,3-diphosphoglycerate (2,3-DPG) resulting in an increase in oxygen affinity and decrease in the cells' ability to unload oxygen to tissues.. The red cell storage lesion-induced changes may functionally limit the ability of the cells to travel through fine capillary networks and unload oxygen in the peripheral circulation resulting in poor oxygen delivery.

Table V. Detrimental side-effects of blood transfusion

Early	Late
Circulatory overload	Delayed haemolytic reactions
Coagulopathy	Immunomodulation
Citrate toxicity	Infectious complications
Hyperkalaemia	Viral
Acute haemolytic reactions	Bacterial
Anaphylactic reactions	Protozoal and other
Hypothermia	Graft versus host disease
Transfusion-related acute lung injury	
Febrile reactions	

Leukocytes are also known to have a number of biological effects associated with allogeneic blood transfusion. The potential clinical importance of these effects is the focus on the current debate over the merits of leukocyte depletion. These effects include febrile transfusion reactions, transfusion-related alloimmunisation to platelets, and transfusion-related immunomodulation.

The immunosuppressive effects of blood product transfusion have been recognised since the 1940s. In 1973 Opelz and colleagues[17] showed that renal graft survival in renal transplant recipients was increased by up to 20% in those who had received a transfusion prior to transplantation. This led to policies of deliberate transfusion in transplant recipients which increased the 1-year renal graft survival from 40% to 60%.

The mechanism of immunomodulation is not clearly understood. There are several theories: clonal deletion of T-cells by foreign major histocompatibility complex antigens; tolerance caused by blockage of receptor sites on T-cells preventing response to antigenic stimulation and active suppression of T-helper cells.[17]

Immunomodulation caused by blood product transfusion may be one of the contributing causes of a trend to increased mortality with blood transfusion noted by Herbert and colleagues in the TRICC study.[13] It is important to note that each unit of blood or blood product increases the degree of immunomodulation.[14] Prudent practice would therefore be to limit the minimum number of units of blood to achieve the haematocrit required.

It is also important to appreciate that not all the effects associated with leukocytes are due to the cells themselves, but are related to the production of various inflammatory cytokines released by the leukocytes. Pre-storage leukoreduction is preferable to bedside leukoreduction filters which may cause significant hypotensive events by activation of the bradykinin/kininogen system.

Avoiding blood transfusions

Avoiding blood transfusions where appropriate makes both economic and clinical sense. A variety of strategies exist to help achieve this goal, including the administration of adequate nutritional support, accepting lower transfusion thresholds, avoidance of bone marrow suppression, erythropoietin stimulation of red blood cell production where appropriate,

consideration of therapy with blood substitutes, and minimising blood loss from diagnostic phlebotomy.

As discussed previously, decreased red cell production is one of the causes of anaemia observed in the critically ill. In a small randomised, placebo-controlled trial of 160 patients treated with recombinant human erythropoietin red blood cell transfusions were reduced by almost 50% as compared with patients treated with placebo.[18] Recombinant human erythropoietin therapy in critically ill patients will result in a decrease in red cell transfusion and an increase in haemoglobin level. This is consistent with the hypothesis that the anaemia in the critically ill is similar to the anaemia of chronic disease and is characterised, at least in part, by a relative erythropoietin deficiency. However, erythropoietin therapy has yet to be shown to improve clinical outcomes.

Conclusion

Anaemia is common in the critically ill patient and results in a large number of blood transfusions. Overall, there is little evidence that 'routine' transfusion of stored allogeneic blood is beneficial to critically ill patients. Based on the available evidence the following recommendations have been made.[19] For critically ill patients who are not actively bleeding and without cardiovascular disease, a haemoglobin level of 7.0 g/dl is acceptable. The exception to this may be the patient with active ischaemic cardiac disease in whom a higher transfusion trigger would be appropriate. Leukocyte-depleted blood probably has no clear advantage over non-leukocyte-depleted blood. Strategies to minimise the loss of blood and to increase erythropoiesis may also be important in the management of all critically ill patients.

1. Corwin HC, Parsonnet KC, Gettinger A. RBC transfusion in the ICU: Is there a reason? *Chest* 1995; **108:** 767–771.
2. Corwin HL, Abraham E, Fink MP, *et al.* Anaemia and blood transfusion in the critically ill: Current clinical practice in the US. *Crit Care Med* 2001; 29: Suppl, A3.
3. Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med* 2003; **31:** Suppl. S651-S657.
4. Low LL, Harrington GR, Stoltzfus DP. The effect of arterial lines on blood-drawing practices and costs in intensive care units. *Chest* 1995; **108:** 216-219.
5. Hameed SM, Aird WC, Cohn SM. Oxygen delivery. *Crit Care Med* 2003; **31:** Suppl., S658-S667.
6. Hébert PC, Szick S. The anemic patient in the intensive care unit: How much does the heart tolerate? *Curr Opin Crit Care* 2000; **6:** 372-380.
7. Ronco JJ, Fenwick JC, Tweeddale MG, *et al.* Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and non septic humans. *JAMA* 1993; **270:** 1724-1730.
8. Carson JL, Duff A, Poses RM, *et al.* Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348:** 1055-1060.
9. Carson JL, Noveck H, Berlin JA, *et al.* Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002; **42:** 812-818.
10. Hebert PC, Wells G, Tweeddale M, *et al.* Does transfusion practice affect mortality in critically ill patients? *Am J Respir Crit Care Med* 1997; **155:** 1618-1623.
11. Wu WC, Rathore SS, Wang Y, *et al.* Blood transfusion in elderly patient's with acute myocardial infarction. *N Engl J Med* 2001; **345:** 1230-1236.
12. Carson JL, Duff A, Berlin JA, *et al.* Perioperative blood transfusion and postoperative mortality. *JAMA* 1998; **279:** 199-205.
13. Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340:** 409-417.
14. Corwin HL, Gettinger A, Pearl RG, *et al.* The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. *Crit Care Med* 2004; **32:** 39-52.
15. Taylor RW, Manganaro L, O'Brien J, *et al.* Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002; **30:** 2249-2254.
16. Rivers E, Nguyen B, Havstad MA, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345:** 1368-1377.
17. Opelz G, Sengar DP, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. *Transplant Proc* 1973; **5:** 253-259.
18. Corwin HL, Gettinger A, Rodriguez RM, *et al.* Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; **27:** 2346-2350.
19. Corwin HL, Surgenor SD, Gettinger A. Transfusion practice in the critically ill. *Crit Care Med* 2003; **31:** Suppl, s668-s671.