Transfusion Medicine 1

Red blood cell transfusion in clinical practice

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Every year, about 75 million units of blood are collected worldwide. Red blood cell (RBC) transfusion is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply. Although the respiratory function of blood has been studied intensively, the trigger for RBC transfusion remains controversial, and doctors rely primarily on clinical experience. Laboratory assays that indicate failing tissue oxygenation would be ideal to guide the need for transfusion, but none has proved easy, reproducible, and sensitive to regional tissue hypoxia. The clinical importance of the RBCs storage lesion (ie, the time-dependent metabolic, biochemical, and molecular changes that stored blood cells undergo) is poorly understood. RBCs can be filtered, washed, frozen, or irradiated for specific indications. Donor screening and testing have dramatically reduced infectious risks in the developed world, but infection remains a major hazard in developing countries, where 13 million units of blood are not tested for HIV or hepatitis viruses. Pathogen inactivation techniques are in clinical trials for RBCs, but none is available for use. Despite serious immunological and non-immunological complications, RBC transfusion holds a therapeutic index that exceeds that of many common medications.

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This is the first in a **Series** of three papers about transfusion medicine

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Introduction

After the first successful human blood transfusions in the 17th century, James Blundell, the English obstetrician who undertook some of the early procedures, cautioned that blood transfusion should be reserved for emergencies.[1] Half of Blundell's first ten transfusion recipients died. One can only wonder how many of his patients might have been saved by appropriate transfusion, how many benefited from the small increments in oxygen-carrying capacity they received, and how many succumbed to transfusion-related complications.

Modern transfusion began with the identification of the major blood groups in 1901 and subsequent use of the agglutination technique for compatibility testing in 1907.[2] The development of anticoagulant-preservative solutions led to the establishment of World War I blood depots in British Casualty Clearing Stations.[3] The quality of these early red blood cell (RBC) components was not well documented, but by all accounts, war-time transfusions saved lives.[4] Clinicians now have an array of RBC components, and the physiology of oxygen delivery has been researched extensively. However, the decision to begin blood transfusion remains controversial.

Whole blood and RBCs

Whole blood (450–500 mL per unit) is collected for refrigerated storage into plastic packs with pre-measured anticoagulant-preservative.[5] The volume, preservative, haemoglobin content (usually >50 g), and storage interval or "shelf life" differ according to national criteria.[6,7] Plasma proteins and other cells in RBCs preserve differently—for example, platelets and granulocytes in refrigerated blood lose biological function within 48 h. In practice, whole blood is rarely available and used infrequently for situations such as massive bleeding where red cells, volume, and plasma factors are all needed.

Red cell units (RBCs, packed red cells) are prepared by removing plasma from whole blood, often replacing it with an additive solution for improved cell viability during extended storage. These blood additives have proved safe, even for neonates, although little is known about their use in critically ill premature infants requiring massive transfusion.[8] RBC volumes range between 200 mL and 350 mL and the haematocrit from 55% to 80%. One unit of RBCs transfused to an adult should in theory raise the haemoglobin concentration by 1 g/dL.[9] In practice, the effect is more variable, with a lower rise in haemoglobin concentration in patients with splenomegaly and renal insufficiency. The effect is also dependent on the patient's height and weight, the haemoglobin content of the unit, and the age of the cells.[10,11] Similarly, although transfusion of 8–10 mL/kg of RBCs is expected to increase haemoglobin by 3 g/dL in an infant, the effect might be smaller in practice.[12]

Fresh or stored cells: the storage lesion

Erythrocytes age more rapidly during refrigeration than they do in the body.[13] The gold standard for red cell viability is the survival of 75% of injected radiolabelled cells at 24 h—an arbitrary standard that permits a quarter of transfused erythrocytes to be non-viable. Time-dependent

Search strategy and selection criteria

We identified reports by searching Medline (1960–2006) with the following MeSH subject headings: "erythrocyte transfusion", "blood component transfusion", "blood transfusion", and "erythrocytes/transplantation". The terms were combined using the Boolean operator "OR" since the MeSH term "erythrocyte transfusion" was previously indexed in Medline as "blood component transfusion" (1992–93), "blood transfusion" (1969–92), and "erythrocytes/transplantation" (1968–92). Search results were restricted to include only English language papers. We searched the PubMed database with the keywords "red cells", "transfusion", and "transfusion reaction". Articles were selected on the basis of the best available evidence for each topic.

Technique	Purpose	Indications	Comments
Leukoreduction			
Filtration of component after collection or at bedside for a 3-log reduction (99·9%) of white blood cells (WBCs); final WBC content <5x10^6	Reduction of febrile non-haemolytic transfusion reactions (FNHTR); reduction of cytomegalovirus (CMV) transmission (CMV-safe); and reduction of HLA alloimmunisation	Patients who have had an episode of FNHTR; as an alternative to donor units tested negative for CMV; neonates; and transplant patients	Not effective for prevention of transfusion-associated graft-versus-host disease
Irradiation			
Irradiation of component with 2500 cGy (centigray) to inactivate lymphocytes	Prevention of transfusion-associated graft-versus-host disease	Recipients of allogeneic hematopoietic transplants; transfusion to blood relatives; patients on immunosuppressive regimens; congenital immunodeficiencies; malignancies; in utero transfusion, and premature infants	Does not reduce infectious risks or prevent FNHTR; unnecessary for aplastic anaemia or HIV-infected patients in the absence of other indications for irradiation
Washing			
Component washed with saline to remove >98% of plasma proteins, electrolytes, and antibodies; WBC content 5X10^8	Prevent allergic reactions; decrease risk of hyperkalaemia	Recurrent severe allergic reactions (not responsive to premedication with antihistamines); IgA or haptoglobin-deficient patients when component from deficient donor is not available; recipients at risk from hyperkalaemia: newborns; and intrauterine transfusions	Washing results in a 15–20% loss of red cells; and not equivalent to leukoreduction
Volume-reduction			
Removal of suspending plasma	Reduction of volume to reduce circulatory overload	Patients who have plasma volume expansion; normovolaemic chronic anaemia; thalassemia major; sickle-cell disease; congestive heart failure; and children, the elderly, and others susceptible to volume overload	Not equivalent to washing for prevention of allergic reactions
Freezing			
Addition of glycerol for cryopreservation	Long-term storage of autologous or rare allogeneic blood phenotypes; and strategic blood depots	Patients with rare blood phenotypes or multiple alloantibodies	Might not be feasible for RBCs with abnormalities such as haemoglobin S or hereditary spherocytosis; not equivalent to leukoreduction (might remove >95% of WBCs); depending on the method of freezing used, the post-thaw shelf-life might be 24 h or 2 weeks; thaw-wash process is lengthy—this component is not suited to emergency supply of multiple units

Table 1: **Indications for modifications of red-cell components**

changes in RBC quality and quantity are commonly referred to as the storage lesion. In storage, adenosine triphosphate (ATP) declines with time, resulting in changes in red-cell shape, and decline in membrane lipid content and cell rigidity.[14–16] Other changes also occur in storage: cells metabolise the glucose in the preservative solution, lactate is produced, pH starts to fall, potassium increases in the suspending medium, free haemoglobin and iron are released from haemolysed red cells, and membrane lipid is shed in the form of vesicles.[17–20] The organic phosphate that binds to deoxyhaemoglobin and facilitates oxygen delivery, 2,3-diphosphoglycerate (DPG), becomes undetectable by week 1 of RBC storage.[21,22] After transfusion of DPG-depleted cells, haemoglobin affinity for oxygen rises significantly. These observations have raised concerns that stored RBCs might not deliver sufficient oxygen to critically ill patients. However, the clinical impact of DPG loss has been difficult to show, perhaps because DPG is regenerated in vivo and nearly restored within a day of transfusion.[23]

A few observational studies suggest that the storage lesion could be responsible for transfusion-associated complications such as immunosuppression and multiple organ failure syndrome.[24,25] However, these reports suffer from the limitations of retrospective analyses.[26] In animal studies, plasma from stored red cells caused vasoconstriction and lung injury.[27] One study of critically ill patients reported a fall in gastric mucosal pH, an indicator of splanchnic hypoxia, after transfusion of RBCs stored for more than 15 days, but a later study failed to confirm these findings.[28,29] In one study, RBCs stored for 3 weeks were as effective as fresh cells (3·5-h old) in reversing the neurocognitive deficit of acute anaemia.[30] With the exception of massive or exchange transfusion for neonates, where excess potassium in stored RBCs can be toxic, little clinical evidence exists to support the notion that fresh RBCs (ie, taken fewer than 7 days before transfusion) is better than stored blood.[8]

RBC compatibility, and modifications to RBCs

Compatibility testing is designed to ensure that the patient receives the intended units of RBCs and that transfusion will be effective with minimum risk of an adverse reaction.[5] The process includes ABO and Rh typing of donor and recipient, testing recipient serum for clinically important alloantibodies, and crossmatching donor red cells with recipient serum by a technique that detects serological incompatibility. Many laboratories now use computer

software instead of the serological crossmatch method.[31] Since most fatal reactions are caused by incompatibilities in the ABO system, ABO typing alone can provide safe blood in an emergency. For the most urgent cases, group O Rh-negative (or "universal donor") blood is issued, and compatibility testing is completed after the fact. RBCs can be modified by filtration, washing, irradiation and cryopreservation for special indications (table 1).

Respiratory function of RBCs

Few clinical signs or symptoms reliably predict early tissue hypoxia, and not many physicians will wait for hypotension, oliguria, or impaired consciousness before starting treatment. Assays that indicate failing tissue oxygenation during acute blood loss or chronic anaemia should guide transfusion need. In practice, however, none has proved easy, reproducible, or sensitive to regional tissue hypoxia. Oxygen delivery from the lungs to the tissues takes place in a complex system in which the erythrocyte functions as the primary intermediary, and compensatory mechanisms overlap. The molecular mechanisms responsible for regulation of microvascular blood flow to meet local tissue oxygen demand are the least well understood component of this system.[32,33]

The respiratory function of red cells, tissue oxygen requirements, and red cell oxygen transport and delivery have been well described.[34] Haemoglobin binds oxygen cooperatively so that small changes in oxygen tension result in large amounts of oxygen being taken up from the lung or released to the tissues. The oxygen-haemoglobin dissociation curve shows the relation between the oxygen saturation of haemoglobin and oxygen tension (figure 1). Oxygen uptake and release are affected by local tissue pH and carbon dioxide concentration as well as by DPG binding. The steep portion of the curve indicates that oxygen tension is well preserved even if oxygen-haemoglobin saturation falls precipitously. This results in the continued delivery of oxygen to the tissues despite progressively lower levels of saturation.[35] Shifts in the P50, the partial pressure at which haemoglobin is 50% saturated, compensate for changes in oxygen tension in the pulmonary alveolus or at the tissue level.

Principles of oxygen transport

Acute loss of about 20% of blood volume elicits compensatory increases in heart rate and cardiac output, as well as a rise in vasoactive hormones, redistribution of blood flow, and influx of extravascular fluid to the intravascular compartment.[36–39] Acute blood loss is managed initially by restoring volume to avoid haemorrhagic shock. Infusions and fluid shifts result in an abrupt decrease in haemoglobin. As haemoglobin falls, compensatory mechanisms reach their limits in the different organ systems. These mechanisms are also less effective in people who are ill or elderly.

Oxygen is transported while bound to haemoglobin, and is dissolved in plasma. The solubility of oxygen in plasma

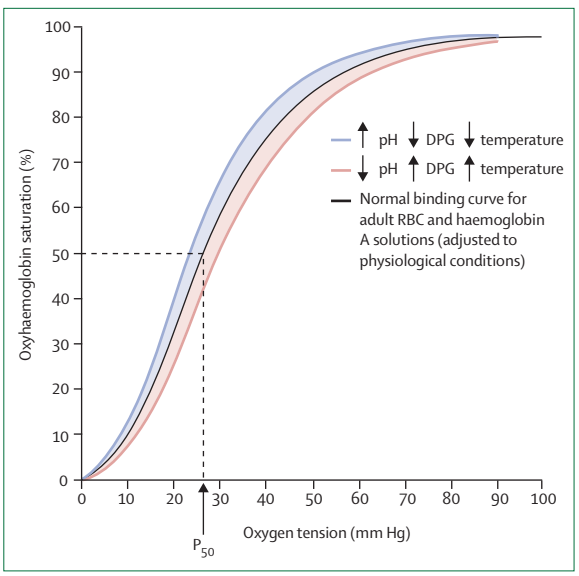

Figure 1: **The oxygen-haemoglobin dissociation curve**
P50=the oxygen tension at which oxyhaemoglobin is 50% saturated.

is low and transport by diffusion is inefficient.[40] Arterial oxygen content (CaO_2) is calculated according to the panel. In non-anaemic patients with a haemoglobin of 14 g/dL and breathing room air, most oxygen is haemoglobin-bound; only 2% is dissolved in the plasma. By contrast, in a severely anaemic patient with a haemoglobin of 5 g/dL and breathing 100% oxygen, 20% of oxygen is dissolved in the plasma. The panel shows equations for the calculation of oxygen delivery (DO_2), which is the product of cardiac output and CaO_2; oxygen consumption (VO_2), the product of cardiac output and the arterial-venous difference in oxygen content; and the relation between oxygen consumption, cardiac output, haemoglobin, and oxygen extraction.

A decrease in the haemoglobin concentration does not necessarily result in reduced DO_2 because cardiac output usually increases. A second global compensatory mechanism involves increasing oxygen extraction, which lowers venous oxygen saturation and partial pressure. With these two mechanisms, normovolaemic patients can tolerate haemoglobin concentrations as low as 5 g/dL without a reduction in VO_2 or signs of impaired oxygenation (figure 2).[41] In addition, at low haemoglobin concentrations, blood flow is redistributed to maintain oxygenation of heart, and brain, and other key organs and tissues.[46]

Panel: **Oxygen delivery and consumption**

$CaO_2=(Hb\times1{\cdot}34\times SaO_2)+(PaO_2\times0{\cdot}003)$

$DO_2=\text{cardiac output}\times CaO_2$

$VO_2=\text{cardiac output}\times(CaO_2-CvO_2)$

$VO_2=\text{cardicac output}\times([Hb\times1{\cdot}34\times(SaO_2-SvO_2)+(PaO_2-PvO_2)\times0{\cdot}003])$

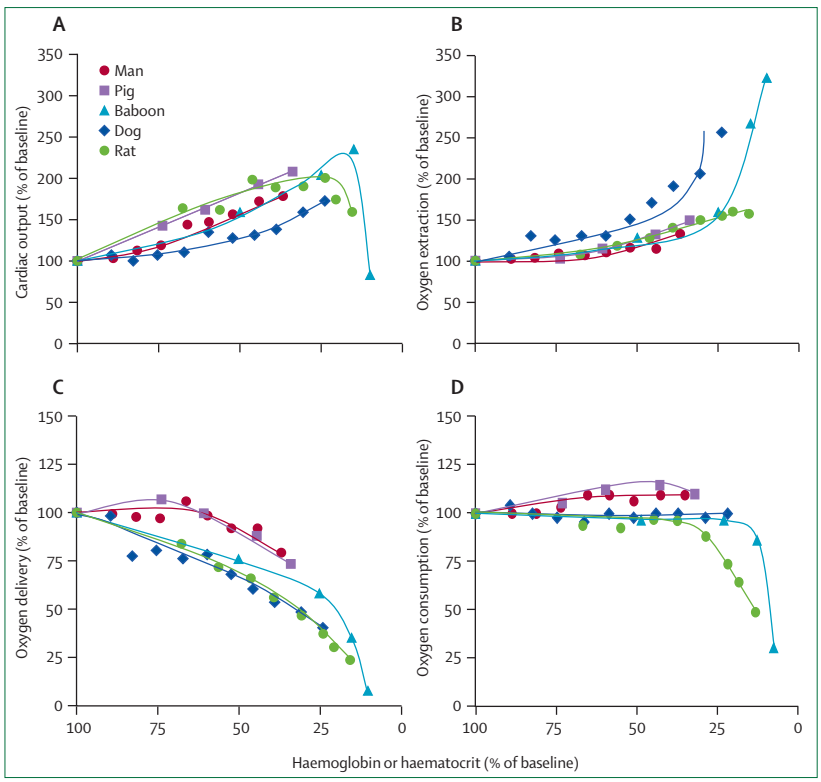

Figure 2: **Relative changes in cardiac output (A) oxygen extraction (B), oxygen delivery (C), and oxygen consumption (D) as haemoglobin concentration decreases in humans, pigs, baboons, dogs, and rats**
The combined increases in cardiac output and oxygen extraction allow maintainance of oxygen consumption until low haemoglobin levels. At extremely low haemoglobin levels, cardiac output and oxygen consumption can fall, indicating the exhaustion of the compensatory mechanisms. Data are from the original articles,[41–45] the curves were approximated.

Physiological adaptation to progressive normovolaemic anaemia

Progressive anaemia results in reduction of blood viscosity, which favours venous return to the heart and facilitates ejection of stroke volume.[41,47] In addition, normovolaemic anaemia increases sympathetic stimulation of the heart, which contributes to the increase of cardiac output during anaemia.[48] In anaesthetised patients, the increase in cardiac output results almost exclusively from an increase in stroke volume,[49–51] while in conscious individuals, heart rate increases as well.[41,49,50] The increase in cardiac output is greater in awake patients than in those who are anaesthetised.[49,50] An increase in heart rate in an anaesthetised patient should be interpreted as evidence of hypovolaemia rather than as compensation for acute development of anaemia.[52] DO_2 decreases during progressive normovolaemic anaemia despite an increase in cardiac output.[41] However, oxygen extraction also increases[41,49–51] and thus VO_2 remains constant in awake patients, even at haemoglobin of 5 g/dL.[41] Both awake and anaesthetised patients tolerate progressive anaemia well. Awake patients compensate primarily by boosting cardiac output, whereas anaesthetised patients also increase oxygen extraction.[41,44,49–51,53]

The limits of compensation

One approach to deciding when to transfuse RBCs compares oxygen delivery with oxygen consumption and defines a "critical haemoglobin concentration"—the point at which compensatory mechanisms for anaemia have been maximised and further reduction in haemoglobin would result in compromised cellular metabolism.[54]

As haematocrit falls, oxygen consumption remains unchanged until a critical DO_2 ($CO \times CaO_2$) is reached where cardiac output and extraction compensation can increase no further and oxygen consumption begins to drop. VO_2 is limited by demand above critical DO_2, and limited by supply below it (figure 2). Patients are in serious danger of organ failure if DO_2 drops below this critical value.

The critical haemoglobin threshold is similar in healthy animals of different species (figure 2).[42,44,53–58] In healthy humans, the critical haemoglobin is unknown but certainly below 5 g/dL.[41,59,60] With normovolemic anaemia, cognitive and memory functions may be impaired before effects on the global circulation appear.[41,61] Acutely decreasing the haemoglobin to 5 g/dL in healthy volunteers results in no signs of circulatory insufficiency. Cognitive function, however, starts to decline reversibly at 6 g/dL; at 5 g/dL immediate and delayed memory are impaired.[61] This subtle dysfunction reverses immediately with transfusion to raise haemoglobin to 7 g/dL[61] or on breathing oxygen.[62] Whereas studies of anaesthetised animals and healthy volunteers define a critical hemoglobin concentration, these studies include no margin of safety for patients with significant medical debility whose compensatory mechanisms might be further compromised by medications, sepsis, trauma or other disorders.

Moderate isovolemic haemodilution is well-tolerated in elderly patients (aged 65–88 years) with no known cardiac disease.[51] Elderly patients can tolerate a reduction in haemoglobin to 9 g/dL, and maintain VO_2 by increasing cardiac output and oxygen extraction as effectively as younger people. Autologous blood was re-transfused at a median haemoglobin of 7·7 g/dL and at a haemoglobin <7 g/dL in nine of 20 patients. No signs of circulatory instability or myocardial ischemia were noted In addition, in patients undergoing coronary artery bypass surgery, compensatory mechanisms were largely independent of age.[50] In a retrospective chart review, the haemodynamic response to a blood transfusion after cardiovascular surgery was not affected by age.[63]

Correction of anaemia in uraemic patients is associated with an improvement in haemostasis, and the acute removal of two units of RBCs results in an increase in the bleeding time.[64,65] By contrast, the effect of acute anaemia on blood coagulation in the perioperative and trauma setting is less clear.[64] For trauma and surgery, a haemoglobin of 7–8 g/dL may represent a reasonable balance between limiting RBCs transfusion and compromising blood coagulation.[66]

Indications for RBC transfusion

Despite extensive physiological data, indications for RBCs transfusion are controversial. Before the 1980s, most perioperative transfusion protocols used the "10/30 rule," which held that haemoglobin must exceed 10 g/dL and haematocrit should be higher than 30% before operation.[67] This recommendation, intended for high-risk anaesthesia patients, was later applied to all transfusion settings, acute or chronic, and became synonymous with the single haemoglobin value 10 g/dL at which transfusion is indicated. Similarly, the term "transfusion trigger," coined to describe factors that motivate physicians to order blood, has become equated with critical haemoglobin value.[68,69] An "optimal" haematocrit has been calculated, and experimental data suggest that 35% represents the best combination of cardiac output and haematocrit in healthy animals and humans.[70] But patients are rarely healthy. One value, however convenient, is unlikely to prove optimal for all conditions.[70]

RBC transfusion is administered most often to surgical and intensive care patients.[71–73] Most studies assessing transfusion thresholds are non-randomised cohort studies, the results of which should be interpreted cautiously; obtaining unbiased results is probably impossible. Observational studies suffer from uncontrolled confounding because blood transfusion is itself an independent marker of disease severity. How many patients need transfusion but are not given it is not known, but studies of diverse patient groups such as children with malaria, people who refuse transfusion for religious reasons, trauma patients, and elderly patients with acute myocardial infarction suggest that the number could be high.[74–78]

Transfusion during intensive care

The Transfusion Requirement in Critical Care (TRICC) is the largest and most widely cited clinical trial evaluating RBC transfusion thresholds.[79] The TRICC investigators randomly allocated 838 adults with haemoglobin lower than 9 g/dL to two transfusion groups.[79] The "liberal" transfusion group received enough blood to maintain haemoglobin at 10–12 g/dL. The "restrictive" group received blood when the haemoglobin fell below 7 g/dL to maintain the haemoglobin at 7–9 g/dL. The primary outcome was 30 day mortality (table 2).

30-day mortality was 23·3% in the group with higher maintained haemoglobin concentrations and 18·7% in the other (p=0·10). There were no significant differences between groups in long-term mortality, infections, or days on ventilator.[79,80] However, the group with lower haemoglobin had a lower rate of myocardial infarction and congestive heart failure than the higher haemoglobin group. A large observational study recorded similar results.[71]

This year, results were published of a trial in children in the intensive care unit. The researchers compared a 7 g/dL threshold on the rate of multiple organ dysfunction with a 9·5 g/dL threshold.[81] As with the TRICC trial, outcomes were much the same in patients allocated to liberal transfusion threshold and restrictive transfusion, and was associated with a 44% drop in the number of red-cell transfusions. These combined findings suggest that many patients in intensive care units are receiving more RBCs than is necessary, although it is unclear how these findings apply to other clinical settings.

Perioperative RBC transfusion

Careful preoperative preparation for elective surgery and use of other blood management techniques reduce the need for allogeneic blood transfusion. Undiagnosed anaemia might be detected first during preadmission testing and is common in the elderly.[82,83] The lower the preoperative haemoglobin concentration, the more likely that a patient will be transfused in the preoperative period. Unsuspected anaemia before elective surgery should prompt a diagnostic evaluation and, if possible, correction of the underlying cause.

Autologous transfusion

With preoperative autologous RBC donation, patients donate up to several units of blood before surgery and then receive their own stored blood during or after operation. The underlying assumption is that transfusing a patient's own blood carries a reduced risk of infectious and immunological complications, and that the patient regenerates some of the blood stored, resulting in less allogeneic transfusion. Meta-analysis of clinical trials confirms a 40% reduction of allogeneic blood transfusion.[84] However, autologous pre-donation is associated with a 30% increase in the need for transfusion (whether allogeneic or autologous), with 80% of patients needing to be given at least one unit of blood.

Other problems with pre-donation autologous storage include the risk of an adverse event during donation, accidental administration of the wrong unit, and the risk of bacterial contamination at least as high as that with allogeneic blood.[85–88] In addition, the patient still receives stored blood with low DPG levels and other changes due to storage. Studies of autologous transfusion have used different transfusion protocols, which makes comparisons of reduction in allogeneic transfusion problematic.

Acute normovolaemic haemodilution involves the removal of a large volume of blood at the start of inducing

	Restrictive n=418	Liberal n=420	p
30-day mortality	18·7%	23·3%	0·11
Long-term mortality	22·7%	26·5%	0·23
Myocardial infarction	0·07%	2·9%	0·02
Congestive heart failure	5·3%	10·7%	<0·01
Pneumonia	20·8%	20·5%	0·92
Other infections	10·0%	11·9%	0·38
Length of hospitalisation	34·8 days	35·5 days	0·58

Table 2: **Selected results from the Transfusion Requirement in Critical Care (TRICC) trial**

anesthesia, and replacing this volume with crystalloid. The blood is re-infused after the surgical procedure is completed, and haemostasis is established. A meta-analysis of 42 trials recorded that the frequency of a patient receiving allogeneic transfusion was not lower than that of patients receiving usual care, although patients who did receive a transfusion used 1–2 fewer units of blood.[89] Cell salvage involves re-infusion of blood shed during a surgical procedure. Meta-analysis of clinical trials indicates that cell salvage reduces allogeneic blood transfusion exposure.[90] Whereas no significant adverse effects have been shown in clinical trials, the average reduction in transfusion needed tends to be small.[91] Cell salvage is most effective in surgical procedures associated with very large blood loss volume.[92,93]

Allogeneic transfusion

Clinical trials evaluating allogeneic transfusions in surgical patients provide little guidance for transfusion practice because most are small[94–99] or include healthy patients with low frequency of adverse outcomes.[100] Two large observational studies of RBC transfusion in surgical patients reached opposing conclusions. A study in 8787 hip-fracture patients that investigated the association between postoperative transfusion, and mortality and morbidity found neither harm nor benefit from postoperative transfusion at haemoglobin triggers of higher than 10 g/dL or lower than 8·0 g/dL.[101] By contrast, a study in 2202 patients undergoing coronary artery bypass surgery reported more frequent postoperative infarcts in patients with higher postoperative haematocrit than in those with an intermediate or low haematocrit.[102] The proportion of transfused patients in the groups was similar.

Patients with cardiovascular disease

In healthy patients, coronary blood flow increases greatly during acute anaemia to compensate for the decrease in CaO_2. Cardiovascular disease could increase the risk from anaemia because of restricted oxygen delivery to the myocardium.[103–107] This concern is supported by results from a study[76] in surgical patients who refuse blood transfusion for religious reasons—irrespective of haemoglobin concentration, patients with cardiovascular disease had a greater risk of dying than those without it. Two small studies found higher cardiovascular events in patients with haematocrit less than 28%.[75,108] In other studies, however, patients with severe coronary artery disease tolerated acute reductions of haemoglobin to 10 g/dL[46] or 8–9 g/dL.[109,110] In a study of patients undergoing surgery for hip fracture, the association of transfusion and mortality did not differ between the 3783 patients with cardiovascular disease and the 5004 patients with no disease.[101] A sub-group analysis of the TRICC trial noted that a restrictive RBCs transfusion strategy seemed safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina.[111]

Three large observational studies have investigated the association between transfusion and outcome in patients with acute myocardial infarction or acute coronary syndrome. Each study reached a different conclusion. In an analysis of US Medicare billing data, the association between haematocrit at admission to hospital and death was assessed in 78 000 patients with acute myocardial infarction.[77] In those with a haematocrit lower than 33%, transfusion was associated with a reduction in mortality. In a study of bleeding patients enrolled in three clinical trials of thrombolytic therapy in acute coronary syndrome, transfusion was associated with increased risk of death and acute myocardial infarction or death.[112] A third study of acute coronary syndrome recorded different results in patients with ST-segment elevated myocardial infarction and non ST-segment myocardial infarction. Blood transfusion was associated with reduced risk of cardiovascular death in the former, but an increased risk of adverse outcome in the latter.[113]

Compromised myocardial contractility might limit the tolerance of acute anaemia, at least in animals,[47] although there are few clinical data to support this. In one group of patients with severe coronary artery disease and a left ventricular ejection fraction between 26% and 83%, there was no correlation between low ejection fraction and inability to increase cardiac output.[50] In dogs, regional contractile dysfunction induced by haemodilution is reversible with minimal RBC transfusion.[114]

Chronic anaemia

In chronic anaemia, increased cardiac output, an increase in red cell DPG, and redistribution of blood flow compensate for the reduced capacity of the blood to carry oxygen.[104–115] Cardiac output is inversely related to haemoglobin. The symptoms of anaemia include fatigue, weakness, dizziness, and reduced exercise tolerance. Transfusion is not usually indicated for these symptoms unless the haemoglobin is so low that the patient cannot function until specific treatment reverses the anaemia.[116,117] Rapid respiration and shortness of breath are signs of oxygen deficit and evidence of cardiac decompensation. Progression to changes in mental activity and muscle cramps indicates severe oxygen deprivation that presages coma and death. For children with severe anaemia related to malaria, RBC transfusion saves lives.[74] Eight (89%) of nine children with haemoglobin lower than than 4 g/dL who were not transfused died, whereas 50 (80%) of 65 who received RBCs survived. Patients vary in their ability to tolerate different levels of anaemia. Those with angina or severe congestive heart failure precipitated by anaemia should be transfused.

The goal of RBC transfusion for congenital anaemia is to maintain normal growth, development, and quality of life, while minimising the adverse effects of recurrent transfusion. For patients with thalassaemia major, modest transfusion to a level of 9–10 g/dL will prevent signs and symptoms of anaemia, and suppress uncontrolled erythropoiesis with its accompanying irreversible bone

deformities.[118] For patients with sickle-cell disease, transfusion to a concentration of 10 g/dL is as effective as more aggressive regimens in preventing the complications of surgery.[119,120] Chronic transfusion reduces stroke by 90% in children at high risk[121] and should be maintained indefinitely. Only anecdotal data exist to support the use of RBC transfusion for patients with other complications of sickle-cell disease.[122] Chronic transfusion did not reduce the complications of pregnancy in women with the disease.[123] Patients with sickle-cell disease on chronic transfusion regimens might benefit from extended typing of their red cells, which can reduce the alloimmunisation rate and the frequency of haemolytic transfusion reactions.[124]

Adverse events associated with RBC transfusion

Transfusion safety involves both the quality of the RBC component and the integrity of the transfusion process from donor collection through administration of the blood. Although the safety of RBC transfusion has improved dramatically during the past 50 years, major risks remain (table 3). Some adverse events such as acute haemolysis occur after only a few millilitres of blood are transfused, while others, such as transfusional haemosiderosis and variant Creutzfeldt-Jakob disease (vCJD) may not become apparent for years. No method has been licensed for inactivation of pathogens in RBCs.[125]

Immune-mediated reactions

The frequency of acute haemolytic reactions has changed little in the past quarter of a century and is calculated at 1 in 18 000 with mortality between 1 in 600 000 and 1 in 1 800 000 per unit transfused.[126,127] Accidental transfusion of ABO-incompatible RBCs remains a leading cause of fatal transfusion reactions.[128] The rate of mislabelled and miscollected samples for the transfusion service has been measured at 1000–10 000 times more frequent than the risk of viral infection from blood.[129] In New York State between 1990 and 1998, 1 in 19 000 RBC units were issued to an individual other than the intended patient, and with the incorrect ABO or Rh group.[130] Some hospitals have addressed administration errors by restricting RBC transfusions in the emergency room and surgical suites to type O, while others have investigated electronic bar code identification to improve patient identification.[129,130]

Acute haemolysis results in the rapid intravascular destruction of red cells. The severity of the clinical syndrome probably represents the degree of complement activation and activation of cytokines, and can include fever, back pain, flushing, anxiety, hypotension, and chest pain.[128] Fulminant haemolysis, progression to renal failure, and coagulopathy are danger signs. Non-immune haemolysis from RBCs that are overheated, accidentally frozen, or mixed with hypotonic solutions before infusion can mimic incompatible transfusion. Treatment in all cases should be supportive.

Alloimmunisation from red-cell transfusions occurs at a rate of about 1% per unit transfused.[132] The incidence depends on genetic factors, dose and frequency, the immunogenicity of the antigen, and the degree of immunosuppression.[133] Delayed haemolytic reactions caused by RBCs alloantibodies occur in 1 in 4000–6000 units of red cells transfused.[134] Most of these reactions are either not apparent or are clinically mild and detected by slight jaundice, low-grade fever, and a drop in haemoglobin that occurs a week or two after transfusion.[134,135] However, lethal intravascular haemolysis has been reported.[136]

Recipient immune response to the leucocytes, and less often cytokines in red-cell transfusions, result in the chill-fever reactions commonly referred to as "febrile non-haemolytic transfusion reactions" (FNHTR). FNHTR are common, but under-reported.[137] A prospective study of HIV-infected patients who received 3864 red cell units during 1745 transfusion episodes documented the frequency of fever as 16·8%.[138] Fever associated with transfusion was recorded about four times as often as the hospital attending staff reported it using a voluntary transfusion reaction form. 3·1% of recipients had a fever elevation exceeding 2ºC. Severe reactions are characterised by flushing within 5 min of the start of transfusion, followed by a temperature spike and rigors about 60 min later.[139] Whereas these reactions are often classified as unimportant by attending staff, they are of great concern to the patient and result in delays in transfusion and costs for evaluation. Red cells can be leuko-reduced to reduce FNHTR.

A related, but far more severe pulmonary reaction (transfusion-related acute lung injury [TRALI]) has been associated with leucocyte antibodies in donor blood.[140] The typical reaction is characterised by chills, fever, a non-productive cough, dyspnoea, cyanosis, and hypotension or hypertension occurring within 1–2 h of transfusion.[141] Characteristic radiographic findings include bilateral pulmonary infiltrates, numerous, predominantly perihilar opacities, and infiltration of the lower lung fields without

	Estimated risk
Febrile reaction	1 in 300
Urticaria or other cutaneous reaction	1 in 50–100
RBC alloimmunisation	1 in 100
Mistransfusion	1 in 14 000–19 000
Haemolytic reaction	1 in 6000
Fatal haemolysis	1 in 1 000 000
TRALI	1 in 5000
HIV 1 and HIV2	1 in 2 000 000–3 000 000
Hepatitis B	1 in 100 000–200 000
Hepatitis C	1 in 1 000 000–1 in 2 000 000
HTLV I and II	1 in 641 000
Bacterial contamination	1 in 5 000 000
Malaria	1 in 4 000 000
Anaphylaxis	1 in 20 000–50 000
GvHD	Uncommon
Immunomodulation	Unknown

Table 3: **Estimated risks in transfusion per unit transfused in the USA**

cardiac enlargement or engorgement of the vessels. Unlike pulmonary oedema associated with circulatory overload, central venous pressure and pulmonary wedge pressure are not raised in TRALI. Some 15% of cases present with mild-to-moderate hypotension, typically unresponsive to fluid challenge, and another 15% present with hypertension.[142] The true rate is unknown, but in the USA, TRALI has been estimated to occur once in every 5000 transfusions.[141]

Mild anaphylactoid allergic reactions such as urticaria occur during 3% of transfusions.[143] In a retrospective analysis of 1613 transfusion reactions, allergic reactions accounted for 17%, but of these only 7% were severe, accounting for 1·7% of all transfusion reactions. Allergic reactions occurred with a frequency of 1 in 4124 blood components and 1 in 2338 transfusion episodes.[144] By contrast, IgE-mediated severe anaphylactic reactions following transfusion occur in about 1 in 20 000–47 000 transfusions.[145] These reactions have been attributed historically to anti-IgA occurring in IgA-deficient patients, although antibodies to other proteins such as haptoglobin may prove more important.[146] Reactions can be avoided by administering RBCs drawn from IgA-deficient donors.[147] Whereas the frequency and severity of urticaria can be reduced by antihistamines, no evidence supports pretreatment with steroids, antipyretics, or other medications for any other allergic reaction.

When T-lymphocytes in RBC transfusions engraft in an immunosuppressed recipient, a highly lethal disorder known as transfusion-associated graft-versus-host-disease (TA-GvHD) frequently results.[148] Whereas early reports suggested that TA-GvHD was confined to immunocompromised patients and transfusions between first-degree relatives, immunocompetent patients are clearly at risk.[149] Freshly collected blood predisposes to the disease, which usually occurs 4–30 days after transfusion. In the most severe form of the syndrome, involving multiple organ systems, mortality is high.[150,151] To avoid the risk of GvHD from blood transfusion, the transfused components must be irradiated to inactivate donor lymphocytes.[152,153] Frozen deglycerolised RBCs have been used for premature infants and intrauterine transfusion without evidence of TA-GvHD.

Numerous alterations in circulating immune cells have been reported in patients transfused with allogeneic blood, some persisting for months or longer. The question has been whether these observations represent laboratory curiosities, or whether they reflect a clinically-relevant alteration in recipient immune status, transfusion-related immune modulation (TRIM). The seminal observation that transfusion before renal transplantation improved the survival of cadaver-derived renal allografts suggested that allogeneic RBCs transfusion has a tolerising effect.[154] The role of perioperative blood transfusion in the recurrence of surgically excised tumors and in increasing the risk of postoperative infection has been disputed for decades.[155–158] Several trials suggest leukoreduced RBCs result in fewer postoperative infections and substantial reductions in morbidity and mortality.[159,160] Based on the sum of evidence, TRIM seems likely to be added to the list of unintended effects of allogeneic blood transfusion. The magnitude, importance, causative agents, and patient groups at particular risk have yet to be defined.[161]

Non-immune reactions

Transfusion-associated circulatory overload is neither acknowledged nor reported often enough. Over 7 years, 1 in 3168 patients transfused with RBCs at the Mayo Clinic reportedly had circulatory overload. After a bedside consultation service was introduced, the frequency of reports rose to 1 in 708 patients, the increase undoubtedly related to improved awareness.[162] A separate retrospective analysis in 385 elderly patients who had had orthopaedic surgery detected a volume overload rate of about 1%.[163]

Hypotensive reactions severe enough to require circulatory support have been recorded when bradykinin and angiotensin generated when blood components are exposed to the charged surfaces of leukoreduction filters.[164,165] Filters from several different manufacturers have been implicated. In a study of patients undergoing heart transplantation, 24 episodes of hypotension were noted in 30 patients who received blood components filtered at the bedside.[166] 11 of these were receiving angiotension-converting enzyme (ACE) inhibitors.

Transfusion-related iron overload is a particular risk to chronically transfused patients, and the major cause of death in individuals with thalassemia.[167,168] About 1 mg of iron is contained in each millilitre of RBCs or about 200 mg of iron in each unit of RBCs. Each year of transfusion adds 5–8 g of iron to body stores of chronically transfused patients, accumulating in the skin, heart, liver, and endocrine organs. Iron-related endocrine dysfunction—growth retardation, diabetes, hypothyroidism, and hypogonadism—are irreversible. Two-thirds of patients die from iron-related cardiac disease.[169] Onset of organ dysfunction is variable and not directly related to the degree of iron overload.[170] Subclinical cardiac abnormalities can occur when total body iron reaches as low as 20 g.[171] Iron chelation therapy must be instituted early and aggressively for patients requiring repeated RBC transfusion.[168]

Future directions

Several developments promise to revolutionise RBC transfusion. The genes encoding the major blood group antigens have been cloned, and differences in DNA sequence have been associated with erythrocyte surface antigen expression. Molecular technology has already been used to determine fetal Rh blood group in the maternal circulation. Using a microarray chip format, rapid screening for single-nucleotide polymorphisms (SNPs) in blood group coding sequences has been accomplished and suggests that a new generation of fully automated DNA analysers could replace agglutination for blood typing, for selecting the best donors for patients with multiple

alloantibodies, and even for improved compatibility testing.[172] Integrated microchip arrays or nanotechnology are being developed to enhance rapid screening of donated blood for any number of infectious agents.[173]

Better understanding of microcirculatory control and sensitive measures of tissue hypoxia promises to provide a more objective basis for initiating, continuing, or discontinuing RBC transfusion.[32,33] To circumvent RBC compatibility problems, methods to remove and mask blood group antigens are being investigated.[174,175] Large-scale ex-vivo production of mature human erythrocytes from haematopoietic stem cells has been achieved.[176] Whereas creating tens of millions of RBCs seems improbable, the technology might be useful for rare donor units. Finally, although RBCs substitutes have been unsuccessful until now, new products are now entering late-stage clinical trials and could ultimately prove important for trauma resuscitation and problems with red-cell compatibility.[177]

Conclusion

The physiology of oxygen delivery and clinical data indicate little need to transfuse patients with a haemoglobin of 10 g/dL or higher. Between 8 g/dL and 10 g/dL, the risk of hypoxic organ damage is low for most patients. Patients with a haemoglobin below 6 g/dL are usually at substantial risk, particularly if postoperative or gastrointestinal bleeding is a possibility. The decision to transfuse red cells should be made in conjunction with analysis of volume, pulmonary, cardiovascular, and cerebrovascular status, duration of anaemia, and likelihood of unexpected acute blood loss. Whereas no convincing evidence exists to indicate that mild-to-moderate anaemia contributes to morbidity, neither has any transfusion algorithm proved better than the judgment of a skilled physician at the bedside.

Conflict of interest statement

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