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Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications

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Careful assessment of risks and benefits has to precede each decision on allogeneic red blood cell (RBC) transfusion. Currently, a number of key issues in transfusion medicine are highly controversial, most importantly the influence of different transfusion thresholds on clinical outcome. The aim of this article is to review current evidence on blood transfusions, to highlight 'hot topics' with respect to efficacy, outcome and risks, and to provide the reader with transfusion guidelines. In addition, a brief synopsis of transfusion alternatives will be given. Based on up-to-date information of current evidence, together with clinical knowledge and experience, the physician will be able to make transfusion decisions that bear the lowest risk for the patient.

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Efficacy of allogeneic red blood cell transfusions

A thorough knowledge of oxygen transport and the physiology of anaemia is still considered to be the most important factor in guiding decisions on red blood cell (RBC) transfusions.[31] Thus we emphasize some basic principles.

Oxygen transport

Oxygen supply has to be adequately matched to tissue oxygen needs to ensure aerobic cell respiration. Whole-body oxygen delivery ($D\mathrm{O}_2$) is the product of blood flow or cardiac output (CO) and arterial oxygen content ($C\mathrm{a}_{\mathrm{O}_2}$):

$$D\mathrm{O}_2=\mathrm{CO}\times C\mathrm{a}_{\mathrm{O}_2}$$

where $D\mathrm{O}_2$ is expressed in ml min^{-1}, CO in l min^{-1} and $C\mathrm{a}_{\mathrm{O}_2}$ in ml l^{-1}.

$C\mathrm{a}_{\mathrm{O}_2}$ is the sum of haemoglobin-bound oxygen and oxygen dissolved in plasma:

$$C\mathrm{a}_{\mathrm{O}_2}=(S\mathrm{a}_{\mathrm{O}_2}\times k_1\times[\mathrm{Hb}])+(k_2\times P\mathrm{a}_{\mathrm{O}_2})$$

where $S\mathrm{a}_{\mathrm{O}_2}$ (%) is the arterial oxygen saturation, k_1= 1.34 ml g^{-1} is the oxygen-carrying capacity of haemoglobin, [Hb] (g l^{-1}) is the haemoglobin concentration, k_2=0.23 ml l^{-1} kPa^{-1} is the plasma oxygen dissolution coefficient at body temperature and $P\mathrm{a}_{\mathrm{O}_2}$ (kPa) is the partial pressure of oxygen of arterial blood. Thus the complete formula describing oxygen delivery is

$$D\mathrm{O}_2=\mathrm{CO}\times(\{S\mathrm{a}_{\mathrm{O}_2}\times k_1\times[\mathrm{Hb}]\}+\{k_2\times P\mathrm{a}_{\mathrm{O}_2}\}).$$

Under physiological conditions (when breathing air), most of the oxygen (>98%) is bound to haemoglobin and the amount dissolved in plasma (<2%) is of relatively minor importance. However, in cases of extreme haemodilution, ventilation with 100% oxygen (hyperoxic ventilation) changes this relationship dramatically. Since the plasma compartment in haemodiluted patients is significantly augmented, hyperoxic ventilation will result in a substantial increase in physically dissolved oxygen. It has been shown that at haemoglobin concentrations as low as 3 g dl^{-1}, physically dissolved oxygen contributes up to 74% of oxygen consumption ($V\mathrm{O}_2$)[28] and reduces mortality significantly.[51] Therefore hyperoxic ventilation has been proposed as an additional method of reducing the need for allogeneic RBC transfusions in cases of blood loss.[26]

It is important to note that blood flow, which is one of the key determinants of $D\mathrm{O}_2$, is regulated not only at the level of the central circulation (as represented by CO in the formula above), but also at the regional level (blood flow between organs) and the microcirculatory level (blood flow within organs).[54] Under physiological conditions $D\mathrm{O}_2$ (800–1200 ml min^{-1}) exceeds $V\mathrm{O}_2$ (200–300 ml min^{-1}) by a factor of up to 4, resulting in an oxygen extraction ratio ($\mathrm{O}_2\mathrm{ER}=V\mathrm{O}_2/D\mathrm{O}_2$) of 20–30%. Consequently, even a marked isolated decrease in haemoglobin concentration with all other determinants of $D\mathrm{O}_2$ remaining constant will still result in sufficient $D\mathrm{O}_2$ to meet tissue oxygen requirements. However, below a critical threshold of haemoglobin concentration there will be a decrease not only in $D\mathrm{O}_2$ but also in $V\mathrm{O}_2$. This relationship between $V\mathrm{O}_2$ and $D\mathrm{O}_2$ is referred to as the concept of critical $D\mathrm{O}_2$ ($D\mathrm{O}_{2\mathrm{crit}}$): above

$D\mathrm{O}_{2\mathrm{crit}}$ tissue oxygenation is sufficient as represented by a constant $V\mathrm{O}_2$ which is thus '$D\mathrm{O}_2$ independent'. In contrast, below $D\mathrm{O}_{2\mathrm{crit}}$ oxygen demands are no longer met, resulting in a decrease in $V\mathrm{O}_2$. This state is characterized by a '$V\mathrm{O}_2$–$D\mathrm{O}_2$ dependency' and the development of tissue hypoxia.[40] This leads to an important question: Which physiological mechanisms compensate for a decrease in haemoglobin concentration in anaemia in order to maintain $D\mathrm{O}_2$ above $D\mathrm{O}_{2\mathrm{crit}}$?

Physiological adaptation to normovolaemic anaemia

Surgical blood loss and trauma are major reasons for blood transfusion.[82] One of the main goals in patients with blood loss is to maintain normovolaemia. Therefore we will assume that hypovolaemia has been corrected and will refer to the situation of normovolaemic anaemia.

Adaptative responses to a decrease in haemoglobin concentration include blood flow alterations at the central, regional and microcirculatory level, and a shift in the oxyhaemoglobin dissociation curve. The resulting key determinants for adaptation to anaemia are an increase in CO, redistribution of blood flow between organs and an increase in O_2ER.[54]

Regulation of blood flow at the level of the central circulation is determined by CO. In response to anaemia, the increase in CO is due mainly to two mechanisms: reduced blood viscosity and increased sympathetic stimulation of the heart. The decrease in blood viscosity due to the lower haemoglobin concentration leads to an increased venous return and thus to an increased preload. Another consequence of the lower blood viscosity is a decrease in systemic vascular resistance and afterload.[31] Increased sympathetic activity leads to an increase in myocardial contractility which contributes significantly to increased CO.[27] An increase in the heart rate in response to increased sympathetic activity is only relevant in humans receiving no medication.[40 95] In contrast, in anaesthetized humans the heart rate does not seem to respond to anaemia.[40 76 95] Therefore the increase in CO in response to normovolaemic anaemia in anaesthetized patients is primarily due to an augmented stroke volume, and an increase in heart rate should be considered as a sign of hypovolaemia.

The regional adaptation of blood flow in response to anaemia comprises redistribution from non-vital to vital organs, such as the heart and brain, which is mediated by the adrenergic system. This is especially important for the myocardium which physiologically has a high O_2ER with a relatively small oxygen extraction reserve. Thus, $D\mathrm{O}_2$ to the heart is primarily increased by augmenting coronary blood flow, in contrast with the brain which is also able to increase O_2ER significantly. In addition, in response to the elevated blood flow to the microcirculation, the homogeneity of the capillary bed is augmented. This occurs with respect to both changes over time (temporal heterogeneity) and differences between vessels (spatial heterogeneity), as only about one-third of capillaries are perfused under normal conditions. The resulting homogeneity leads to an increased O_2ER.[54] Finally, owing to increased synthesis of 2,3-diphosphoglycerate (2,3-DPG) in red cells, the oxyhaemoglobin dissociation curve shifts to the right, thus allowing more haemoglobin-bound oxygen to be released at a given oxygen partial pressure.[31]

Rationale and efficacy of RBC transfusions

In view of the mechanisms of adaptation to anaemia, what is the rationale behind RBC transfusions, and is their efficacy proven?

The rationale underlying RBC transfusion should not only aim at increasing $C\mathrm{a}_{\mathrm{O}_2}$ and thus $D\mathrm{O}_2$, but essentially at increasing $V\mathrm{O}_2$, thereby restoring adequate tissue oxygenation.[71] Increasing $D\mathrm{O}_2$ without a concomitant increase in $V\mathrm{O}_2$ would indicate the absence of $V\mathrm{O}_2$–$D\mathrm{O}_2$ dependency and thus any increase in $D\mathrm{O}_2$ would be, strictly from a physiological point of view, of questionable relevance.[71] Hébert and colleagues[30] identified 18 studies examining the effect of RBC transfusions on oxygenation variables. While in all studies there was a significant increase in haemoglobin concentration in response to blood transfusion, in four of them there was no increase in $D\mathrm{O}_2$. Furthermore, in the other 14 studies with an increase in $D\mathrm{O}_2$, a parallel increase in $V\mathrm{O}_2$ was detected in only five.[30] This lack of increase in $V\mathrm{O}_2$ after RBC transfusion could be explained by the absence of an oxygen debt prior to infusion. Indeed, there is evidence from experimental studies that pre-existing $V\mathrm{O}_2$–$D\mathrm{O}_2$ dependency, and thus tissue hypoxia, was followed by an increase in $V\mathrm{O}_2$ after RBC transfusion.[20 59] This prompts us to ask whether there are factors that identify patients who are likely to react favourably, i.e. who increase $V\mathrm{O}_2$ upon RBC transfusion. Casutt and colleagues[13] examined 67 cardiac surgery patients who received a total of 170 RBC transfusions. Measurements were performed approximately 5 h before and after RBC transfusions. It was found that pretransfusion haemoglobin, preoperative ejection fraction and age were unrelated to individual responses in cardiac index (CI), $D\mathrm{O}_2$ and $V\mathrm{O}_2$ after RBC transfusion. In contrast, variables related to oxygen delivery and oxygen consumption correlated with individual responses to RBC transfusions and allowed better prediction with regard to an increase in CI, $D\mathrm{O}_2$ and $V\mathrm{O}_2$. In particular, a low oxygen consumption index correlated very well with an increase in $V\mathrm{O}_2$ after transfusion. Similarly, another study of patients evaluated whole-body O_2ER as a parameter for guiding transfusion decisions.[67] Seventy patients undergoing coronary artery bypass graft (CABG) surgery with a postoperative hematocrit of 25% were included. O_2ER was monitored without influencing transfusion decisions. Retrospectively, it was analysed whether an O_2ER of 45% as a transfusion trigger would have changed decision-making. Of the 41 patients who received at least one allogeneic RBC transfusion, seven had a postoperative

O_2ER of 45%, while only three of the 35 patients who were not transfused reached this physiological transfusion trigger. Thus it was concluded that whole-body O_2ER might be a helpful variable in a transfusion algorithm.[67]

Alternatively, one might argue that impaired functionality of stored RBCs could be a reason for the lack of increase in V_{O_2} after RBC transfusion.[71] During storage, RBCs undergo a variety of changes which are summarized under the term 'storage lesions'.[60] These include a decrease in 2,3-DPG, ATP depletion and the release of proinflammatory substances. This results in a leftward shift of the oxyhaemoglobin dissociation curve (i.e. increased oxygen affinity), impaired RBC deformability and inflammatory reactions in the transfusion recipient.[57 60] In particular, the decrease in 2,3-DPG levels and RBC deformability suggest a decreased efficacy of 'old' RBCs and thus a failure to increase V_{O_2} after transfusion. It has been shown that, after 2 weeks of storage, priming of neutrophils by agents released from RBC units becomes significant.[69] The results of a study of critically ill patients with sepsis[50] are in accordance with this finding. Measurements were made before and after transfusion of three units of RBCs. RBC transfusions did not result in an increase in systemic V_{O_2}. Interestingly, splanchnic ischaemia occurred in patients receiving RBC units that were >15 days old.[50] In a retrospective study, Purdy and colleagues[65] studied 31 critically ill septic patients. It was found that the non-survivors (19 patients), although not differing in the incidence of septic shock, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, intensive care unit (ICU), length of hospital stay (LOS), age and number of RBC units transfused compared with survivors, were transfused with significantly older RBCs (24 versus 21 days, $P<0.0001$). In an analysis of medical records of CABG surgery patients, it was found that the age of RBCs was a predictor for postoperative infection and pneumonia.[87] In contrast, a prospective observational study in cardiac surgery patients could only identify storage for >28 days, but not the mean age of transfused RBC units, as a predictor of pneumonia.[43] However, recent reviews have concluded that current evidence on the effect of storage duration of RBCs is insufficient and that additional trials are necessary.[36 57] Surprisingly, a recent prospective randomized study in 22 critically ill patients did not detect any difference in adverse events after transfusion of RBCs stored for >20 days (mean age 28 days) compared with RBCs stored for <5 days (mean age 2 days). In addition, this study again showed a lack of improvement in tissue oxygenation after RBC transfusion.[93] Owing to the methodological limitations of this single-centre study, it was again stated that large prospective multicentre clinical trials are needed to define the role of RBC age on outcome.[56]

Studies evaluating the outcome of RBC transfusions

Although numerous studies have addressed the effects of RBC transfusions, only one randomized controlled trial (RCT), the Transfusion Requirements in Critical Care (TRICC) Trial,[32] had sufficient power to evaluate the effect of transfusions on morbidity and mortality.[12] This study, conducted by Hébert and colleagues,[32] enrolled 838 critically ill patients who were admitted to the ICU with an initial haemoglobin concentration >9 g dl^{-1}. The patients were randomized to either a restrictive transfusion strategy with a transfusion trigger of 7 g dl^{-1} (target haemoglobin concentration, 7–9 g dl^{-1}) or a liberal transfusion strategy with a transfusion trigger of 10 g dl^{-1} (target haemoglobin concentration, 10–12 g dl^{-1}). Thirty-day mortality was slightly lower in the restrictive transfusion group (18.7% versus 23.3%), although statistical significance was not reached (P=0.11). However, subgroup analyses of patients who where less acutely ill, as defined by the APACHE II score, or who were aged >55 yr showed a significantly lower 30-day mortality in the restrictive transfusion group. In addition to the TRICC trial, Carson and colleagues[12] identified nine other RCTs that used a clearly defined restrictive or liberal transfusion strategy, giving a total number of 1780 patients in 10 trials. Transfusion protocols used in these studies were different, resulting in overlapping transfusion triggers. The clinical settings were also different, which may partly explain the variability in terms of effect size of the clinical outcomes, particularly concerning the effect of restrictive transfusion thresholds on the use of blood transfusions.[12] Apart from the TRICC trial, only two other studies comparing different transfusion thresholds included more than 100 patients.[8 47] However, the differences in postoperative haemoglobin levels were not significantly different[8] or were very small.[47] There was no[47] or very little mortality, which was not significantly different between the two transfusion strategies.[8] Consequently, a meta-analysis of these studies was dominated by the TRICC trial which contributed more than 80% of the observed deaths in the mortality analysis.[12 35] There were also no significant differences in morbidity and LOS.

The results of these RCTs have to be compared with the results of observational studies evaluating the effect of anaemia and blood transfusion strategies on morbidity and mortality. Again, there is a considerable heterogeneity concerning the clinical setting among these studies. Among 10 observational studies conducted to date,[10 15 33 37 58 62 81 90 91 99] the six largest included patients in the ICU,[15 33 90 91] orthopaedic surgery[10] and cardiac surgery.[81] The conclusions are contradictory. The recently published CRIT study (Anaemia and Blood Transfusion in the Critically Ill—Current Clinical Practice in the United States) enrolled 4892 patients from August 2000 to April 2001,[15] 44.1% of whom were transfused with one or more RBC units. Mean pretransfusion haemoglobin was 8.6 (SD1.7) g dl^{-1}. The number of RBC units transfused was an independent risk factor for mortality and LOS. In addition, patients who were transfused had more complications and were more likely to experience complications. A very similar study, the ABC study (Anemia and Blood Transfusion in the

Critically Ill), was performed in European ICUs.[90] Similar to the CRIT study, 37.0% of the 3534 patients (enrolment from November 15 to November 29, 1999) were transfused with a mean pretransfusion haemoglobin of 8.4 (1.7) g dl^{-1}. Mortality was higher for transfused patients than for non-transfused patients with similar organ dysfunction as assessed by the Sequential Organ Failure Assessment (SOFA) score. After matching patients by propensity scores (i.e. probability) for being transfused (and thus controlling, amongst other variables, for SOFA and APACHE II score), 28-day mortality was significantly higher in patients with transfusions (22.7% versus 17.1%, P=0.02). The most recently conducted study, the SOAP study, enrolled 3147 patients between May 1 and May 15, 2002,[91] of whom 33% received an RBC transfusion. Patients receiving transfusions were older and generally sicker. Therefore it is not surprising that mortality rates were higher in transfused patients. Similarly, higher transfusion rates were associated with higher mortality. However, after propensity matching, mortality rates were the same in transfused and non-transfused patients, with a tendency towards lower survival in non-transfused patients. Thus the SOAP study contrasts with the CRIT and ABC studies; this could be due to the implementation of deleucocytation in Europe, as the authors suggested.[91]

The largest observational study included 8787 consecutive hip fracture patients, aged $\geqslant$60 yr, who underwent surgical repair between 1983 and 1993.[10] There was no influence of perioperative RBC transfusion on 30- or 90-day mortality in patients with a haemoglobin concentration $\geqslant$8 g dl^{-1}. The effect of a transfusion on mortality in patients with a haemoglobin concentration <8 g dl^{-1} could not be calculated since 90.5% of these patients, who made up only 12.7% of the whole study population, received a transfusion. In addition to the possibility that potential confounders were missed (a problem which is inherent in all observational studies), the authors identified a number of other limitations that have to be considered when interpreting these results.[10] However, these results indicate that transfusion at haemoglobin levels >8 g dl^{-1} may not improve survival in elderly patients with a high illness burden.

What is the evidence from these RCTs and observational studies?

The validity of the observational studies is not clear because sicker patients are more likely to be transfused.[77] Although statistical analysis tried to control for potentially confounding factors (e.g. in the CRIT and ABC studies), this adjustment could only be made for the variables recorded. Thus, given the complex pathophysiology of critical illness, it is possible that comorbidity was not sufficiently adjusted for in these observational studies. Consequently, they only allow conclusions about associations between factors and not about causality. However, one key question still remains to be answered: Why does there seem to be a relationship between RBC transfusions and worse clinical outcome in some studies such as the CRIT and ABC studies, and why does the more recently conducted SOAP study contradict them?

One issue that is currently under substantial debate is universal leucoreduction.[68] Compared with buffy-coat-free RBCs, the use of a leucocyte filter results in a 3 log reduction of leucocytes to approximately 10^6/RBC unit.[16] The observation that RBC transfusions may be linked to immunosuppression was made more than 30 years ago.[61] Since then, particular interest has been directed towards the contribution of white blood cells (WBCs) to transfusion-associated immunomodulation (TRIM).[7] Numerous observational studies and RCTs have been performed examining the immunomodulatory effect of allogeneic RBC transfusions and the effect of WBC reduction.[86] A meta-analysis of RCTs examining the association between allogeneic RBC transfusion and postoperative infection could find no difference between WBC-reduced and buffy-coat-reduced blood.[84] In contrast, transfusion of non-buffy-coat-reduced allogeneic RBCs (or whole blood) was associated with increased risk for postoperative infection. However, this conclusion was based on three heterogenous studies and therefore was not very convincing, prompting the author to call for further RCTs investigating TRIM of non-buffy-coat-reduced (or whole blood) versus WBC-reduced allogeneic RBC transfusions.[84] A before-and-after cohort study in Canada found a reduction in mortality, post-transfusion fevers and antibiotic use after implementation of a universal leucoreduction programme.[29] In contrast, a recent meta-analysis by Vamvakas[85] did not find an association between WBC-containing allogeneic (compared with WBC-reduced allogeneic or autologous) RBC transfusions and mortality. Subgroup analyses of this meta-analysis suggested that there may be an association between WBC-containing allogeneic RBC transfusions and short-term mortality in the setting of open-heart surgery and when WBC-containing allogeneic RBC transfusions are compared to prestorage-filtered WBC-reduced RBC transfusions.[85] However, these associations were not very strong. A recent prospective cohort-controlled study observed a decrease in LOS in open-heart surgery with leucoreduced blood transfusions.[22] In contrast, a before-and-after study in the UK observed no impact on LOS and postoperative infection in orthopaedic and cardiac surgery,[46] thus adding additional contradictory conclusions to this ongoing debate.

In view of this huge controversy, it is interesting to note that the major difference between the two large European observational studies, the SOAP study and the ABC study, was that leucoreduction was much more common in 2002 than in 1999.[98] At the time of inclusion of the patients for the ABC study, Germany, Holland, Norway and Finland who together contributed about one-third of the 3534 patients, had not started implementation of universal leucoreduction, while other participating countries were just completing it.[98] Additionally, the authors stated that 46% of the ICUs used leucocyte-depleted blood most of the time, 35% some of the

time and 19% never.[90] Thus the contradictory results of these two studies may suggest a possible role of leucocytes in causing adverse clinical outcomes after RBC transfusion. However, this is purely speculative and therefore it will be important to see the outcomes of future large RCTs evaluating different transfusion thresholds, comparable to the TRICC trial but with WBC-reduced blood.

In addition, the age of RBC units may be another important factor influencing the efficacy of RBC transfusion as outlined above. Thus a lack of control of this factor may be another reason for these contradicting results.

Tolerance to anaemia–RBC transfusions in patients at risk

The so-called '10/30 rule', meaning that an RBC transfusion was indicated below a haemoglobin concentration of 10 g dl^{-1} or a haematocrit below 30%, has served as a transfusion trigger for many years. However, on the one hand this rigid numerical transfusion trigger totally neglects individual patient factors and the underlying pathophysiological consequences determining each patient's individual tissue oxygen demands. On the other hand it does not reflect the capacity of human tolerance to anaemia. In a case report of an 84-yr-old Jehovah's Witness, the critical haemoglobin concentration (Hb_{crit}) at which DO_2 was reached was about 4 g dl^{-1}. A review of the literature on Jehovah's Witnesses identified 134 medical and surgical patients with a haemoglobin concentration <8 g dl^{-1} or a haematocrit <24%.[89] Fifty deaths were reported among these 134 patients, of which 23 were attributed exclusively or primarily to anaemia. All these patients, with the exception of three with cardiac disease who died after cardiac surgery and two with missing laboratory data, died with a haemoglobin concentration <5 g dl^{-1} or an equivalent haematocrit. Notably, this value was also found in 27 of the survivors. Weiskopf and colleagues[96] showed in 32 healthy volunteers and patients that acute isovolaemic haemodilution to a haemoglobin concentration <5 g dl^{-1} did not induce an inadequate systemic DO_2. These results further supported the assumption of a critical haemoglobin concentration of $\leqslant$5 g dl^{-1} in healthy human beings. They also support the most recent recommendations defining a haemoglobin concentration <6 g dl^{-1}, which is close to the critical haemoglobin concentration reported in the literature, as a transfusion trigger.[2] Furthermore, in a haemoglobin concentration range of 6–10 g dl^{-1}, they propose an individual assessment of each patient's risk for complications of inadequate oxygenation. A number of clinical risk factors which may decrease a patient's tolerance to anaemia and thus increase the critical haemoglobin concentration have been identified.[48] Patients with coexisting cardiovascular disease (CVD) may be at particular risk. In coronary artery disease (CAD), an adequate increase in the coronary blood flow in response to a decrease in haemoglobin concentration is not possible and myocardial ischaemia may develop. In addition, impaired myocardial contractility may limit the compensatory increase in CO. A retrospective cohort study in 1958 patients who declined blood transfusions for religious reasons corroborated this hypothesis.[11] It was found that below a preoperative haemoglobin concentration of 10–11 g dl^{-1} the mortality increased in patients both with and without CVD, but more in the CVD group. Similarly, in a subgroup analysis of an observational study evaluating the effect of anaemia and blood transfusion strategies on mortality, Hébert and colleagues[33] found an association between anaemia and risk of death in critically ill patients with cardiac disease. They detected an improved survival in this subgroup of patients with increasing haemoglobin values (odds ratio 0.80 [95% CI 0.66–0.97] for each 1.0 g dl^{-1} increase starting from a pretransfusion haemoglobin concentration <9.5 g dl^{-1}, P=0.01). In contrast with these findings, a subgroup analysis of the TRICC trial showed no differences in mortality rate between the restrictive and the liberal transfusion strategies in patients with CVD.[34] Although the authors were aware of the possible limitations of this subgroup analysis, they suggested that a transfusion trigger of 7 g dl^{-1} would be safe in critically ill patients with CVD.[34] Possible exceptions were patients with acute myocardial infarct and unstable angina. Taking these studies together, recent reviews on this topic concluded that Nevertheless, as is necessary in healthy patients, clinical signs of inadequate oxygenation should guide transfusion decisions.[2 74] In the case of patients with CVD, new ST-segment depression >0.1 mV, new ST-segment elevation >0.2 mV or new wall motion abnormalities on transoesophageal echocardiography may represent signs of inadequate oxygenation of the myocardium.[74] However, more studies, particularly large RCTs, are required to clarify transfusion requirements in this important subgroup of patients.

Transfusion-associated risks

Transfusion-related risks can be divided into transfusion-transmissible infections (TTIs), immunological risks and mistransfusion.

Infectious risks

RBC transfusion in Western countries has probably never been safer than today with respect to transfusion-transmissible viruses such as HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV).[49] The estimated risks of infection have dramatically decreased over recent years as increased test sensitivity has reduced the infectious window periods.[23] Estimates of current risk are shown in Table 1.

In contrast with Western countries, viral TTIs are a major problem in countries with a low human development index (HDI), which is an index based on life expectancy, literacy, enrolment in higher education and per capita income (Table 1). A high seroprevalence of these diseases in the general population of these countries, poorly organized

Table 1 Transfusion-associated risks (modified according to Marcucci and colleagues[49])

Type of risk	Estimate of current risk (infection rate per unit)	
	High HDI countries	**Low HDI countries**
Infections		
Viruses		
HIV	1:1 468 000[17]–1:4 700 000[42]	1:50[53]–1:2578[9]
HBV	1:31 000[42]–1:205 000[17]	1:74–1:1000[4]
HCV	1:1 935 000[17]–1:3 100 000[42]	1:2578[9]
Bacteria (contamination)	1:2000–1:8000 (platelet pools)/1:28 000–1:143 000 (red cells)[42]	?
Parasites		
Malaria	1:4 000 000[42]	1:3[41]
Prions		
vCJD	First two possible transmissions described[46 63]	?
Immunological reactions		
Haemolytic transfusion reactions		
Acute haemolytic	1:13 000[42]	?
Delayed haemolytic	1:9000[42]	?
Alloimmunization	1:1600[42]	?
Autoimmunization	? (recently identified as risk)[100]	?
Immunosuppression	1:1[39]	?
TRALI	1:70 000[42]	?
Mistransfusion	1:14 000–1:18 000[23 42]	?

blood donation systems and poor sensitivity of pathogen testing are important factors.[49] Future transfusion practice in low HDI countries will strongly depend on international investment to guarantee appropriate transfusion safety.[5]

Compared with viral TTIs, there is much more concern about transfusion-transmitted bacterial infections (TTBIs) and post-transfusion sepsis[92] in high HDI (Western) countries. Contamination of platelets is more common than transfusion of bacteria-containing RBC units. This is due to the platelet storage temperature of 20–24°C which favours bacterial growth, in contrast with RBCs that are stored at 4°C. Best risk estimates of TTBIs from a Canadian study gave values in the range of about 1:2000 to 1:8000 (13–44 per 100 000) for platelet pools and 1:28 000 to 1:143 000 (0.7–3.6 per 100 000) for transfused RBC units.[42] Notably, when comparing the frequency of TTBIs from different studies, the differing stringency of criteria for the diagnosis of TTBI should be considered.[42]

Variant Creutzfeld–Jakob disease

Recently, the first possible cases of transfusion-transmitted variant Creutzfeld–Jakob disease (vCJD) have been reported.[45 63] The probability that the first case of vCJD was not due to transfusion-transmitted vCJD ranged from 1:15 000 to 1:30 000. The hypothesized incubation period of transfusion-transmitted vCJD was 6.5 yr.[45] The UK's second case of vCJD possibly transmitted by a blood transfusion may have been caused by blood administered in 1999.[63] This patient died of causes unrelated to vCJD. As with the first case, this patient was the recipient of non-leucodepleted RBCs from a donor who developed symptoms of vCJD after donation. A post-mortem examination revealed the presence of prion proteins in the patient's spleen and cervical lymph node but not in gut-associated lymphoid tissue and tonsil, which suggests an intravenous rather than an oral route of transmission.[63] This led the UK government to extend its ban, which initially excluded anyone who had received a blood transfusion since January 1980 from blood donation, to cover a larger group of transfusion recipients.[64] The latest ban, which came into operation in April 2004, has reduced the number of donors in the UK by 3.3%.[1] Since 1999, the pool of blood donors in the UK has fallen by over 20% and currently stands at 1.64 million.[1] The impact of the extended ban, which will become effective from April 2005, remains to be seen. Taking into account the incubation period of 6.5 yr in the first case, asymptomatic vCJD patients with such a long incubation period could represent a significant source of iatrogenic infection by blood donation or contamination of surgical instruments.[63] Interestingly, it has been shown that leucoreduction is efficacious in reducing white-cell-associated transmission of spongiform encephalopathies but fails to eliminate it.[25] In addition, some infectivity of transmissible spongiform encephalopathies (TSEs) is assumed to be plasma associated.[25] The policy of leucoreduction aimed at reducing TSE infectivity may require re-evaluation.

Immunological risks

In contrast with low HDI countries, which are very concerned with TTIs, immunological transfusion reactions are generally more frequently encountered in high HDI countries[49] (Table 1).

As already outlined, RBC transfusions seem to have an immunomodulatory effect, the causes of which are not very well understood. Although several studies have suggested that WBCs cause immunomodulation, the blood components that mediate this effect are still not defined. It is beyond the scope of this review to discuss all immunological risks in detail. Therefore the reader is referred to a comprehensive review on risks associated with RBC

transfusions in Canada.[42] However, the reader's attention should be directed towards one complication that is controversial: transfusion-related acute lung injury (TRALI). According to the Serious Hazards of Transfusion (SHOT) Annual Report,[3] in 2003 there were 36 suspected cases in the UK and RBCs were implicated in five of these. This corresponds to one implicated case per 529 000 RBC units transfused (0.2:100 000 RBC units),[3] whereas Canadian data from 1998 gave a risk estimate of 1.4:100 000 RBC units transfused,[42] and estimates from the USA are as high as 1:5000 RBC units transfused.[24] Thus there is considerable uncertainty as to the incidence of TRALI since under-reporting is thought to be a problem.[42 94] This may be due to lack of awareness or the difficulty in diagnosis, as the symptoms and signs of TRALI may be confused with other conditions such as adult respiratory distress syndrome, volume overload or congestive heart failure. The most urgent issue concerning TRALI is the need for a standardized definition which would allow reliable statements about incidence and comparison between hospitals.[94]

Mistransfusion

Mistransfusion is estimated to occur in 1:14 000 to 1:18 000 transfusions and thus is one of the most frequent transfusion hazards in HDI countries.[23 42 97] To make matters worse, mistransfusion is associated with significant morbidity and mortality.[97]

Transfusion alternatives

As already outlined, allogeneic RBC transfusions bear considerable risks, have possible adverse clinical outcomes and are of questionable efficacy. In addition, they are expensive and susceptible to shortages. Thus blood conservation strategies are crucial for a reduction in the need for allogeneic RBC transfusion.[73] There are different options for the pre-, intra- and postoperative periods.

Preoperatively, autologous blood donation (ABD) and the use of recombinant human erythropoietin (EPO) are of value. ABD has most benefit in patients who undergo surgical procedures with a high estimated blood loss such as orthopaedic joint replacement surgery. In a retrospective study in 9482 patients with total joint (hip and knee) replacement surgery, about 28% of patients who had not predonated blood received allogeneic RBC transfusion compared with only 9% of all the patients having ABD. In the subgroup of mildly anaemic patients (haemoglobin concentration of 10–13 g dl^{-1}) having ABD, the rate of allogeneic RBC transfusions increased to about 15%.[6] However, only 55% of the predonated blood units were given back to the patients,[6] which explains the poor cost-effectiveness of ABD.[18] The stimulant effect of EPO on RBC production starts to become efficacious after 5–7 days. Therefore EPO clearly has its place in the preoperative preparation of the anaemic surgical patient.[66] It reduces the need for allogeneic blood transfusions and can effectively be combined with other blood conservation techniques.[52]

Intraoperatively, acute normovolaemic haemodilution (ANH),[40] cell salvage,[21] pharmacological haemorrhage control,[38] anaesthesia and surgical techniques, acceptance of minimal haemoglobin levels and artificial oxygen carriers[14 73 75] can be used to avoid allogeneic RBC transfusion.[66 73]

Postoperatively, cell salvage, acceptance of minimal haemoglobin levels and pharmacological haemorrhage control can be used.[73]

Transfusion guidelines

As mentioned earlier, haemoglobin-based transfusion triggers do not take into account the individual patient's ability to tolerate and compensate for anaemia. Therefore appropriate transfusion guidelines should be based primarily on physiological transfusion triggers, whereas haemoglobin-based transfusion triggers should serve as an aid in cases of insufficient or unreliable information on the patient's global or regional tissue oxygenation. What are the useful signs of inadequate global or regional tissue oxygenation that can be incorporated into guidelines as physiological transfusion triggers?

Before applying physiological transfusion triggers, it is important to rule out hypovolaemia, optimize anaesthesia, and correct any pre-existing tachycardia. Global signs of inadequate oxygenation are haemodynamic instability with relative tachycardia and hypotension,[72 80] O_2ER>50%,[70 72 78] a mixed venous oxygen saturation ($S\bar{v}_{O_2}$) <50%,[72] a low mixed venous oxygen partial pressure ($P\bar{v}_{O_2}$)[70 72] and a decrease in $V\dot{O}_2$.[70 72] Different thresholds have been proposed for $P\bar{v}_{O_2}$ and $V\dot{O}_2$.[70] In their guidelines, the College of American Pathologists suggested $P\bar{v}_{O_2}$ <25 mm Hg and a decrease of >50% in $V\dot{O}_2$ as physiological transfusion triggers.[70] These transfusion triggers are probably too restrictive, since they have been shown to be reached only after circulatory failure.[55] In accordance with experimental[83] and clinical[88] results, a transfusion trigger of $P\bar{v}_{O_2}$<32 mm Hg seems to reflect better the threshold at which $D\dot{O}_{2crit}$ is reached. Similarly, a decrease in $V\dot{O}_2$ of >10% should serve as a safer transfusion trigger.[73]

With respect to impaired regional oxygenation, there is most concern about myocardial ischaemia. New ST-segment depression >0.1 mV or new ST-segment elevation >0.2 mV for more than 1 min in continuous five-lead ECG monitoring and new wall motion abnormalities detected by transoesophageal echocardiography may be signs of myocardial ischaemia.[74] Importantly, this haemodilution-associated myocardial ischaemia can be reversed by a small increase in haemoglobin concentration[79] or a decrease in heart rate.[44] Transfusion indications based on physiological and numerical transfusion triggers are shown in Table 2.

Conclusions

There is now general agreement that transfusion decisions should be primarily based on an individual patient's need for

Table 2 Haemoglobin-based and physiological transfusion triggers as a function of patient-related and logistical factors (modified according to Marcucci and colleagues[49]). An RBC transfusion is indicated if *one* of the criteria given in the table is reached: Hb threshold, circulation criterion, myocardial ischaemia or one of the oxygenation variables (Pv_{O_2}, O_2ER, Sv_{O_2} or Vo_2). For all physiological transfusion triggers, normovolaemia, optimization of anaesthesia and the correction of tachycardia (if present) is assumed and anaemia should be the only probable cause. *Includes all patients except the subcategories patients aged >80 yr, patients with CAD, patients with CVD and patients with fever/hypermetabolism. †One may choose *not* to transfuse the individual patient without any physiological transfusion triggers. ‡Relative tachycardia is defined as a heart rate >120–130% of baseline or >110–130 bpm; relative hypotension is defined as a mean arterial pressure <70–80% of baseline or <60 mm Hg (<55 mm Hg in young healthy patients, <70–80 mm Hg in patients with CAD or CVD and in hypertensive patients, and even higher in severely hypertensive patients). §New ST-segment depression >0.1 mV or ST-segment elevation >0.2 mV. ¶To be confirmed with ECG and/or troponin measurement if possible in a timely fashion

Situation	Patients	Hb (g dl^{-1})	Circulation	Myocardial ischaemia	Pv_{O_2}<32 mm Hg, O_2ER>50%, Sv_{O_2}<50%, decrease inVo_2>10%
Intraoperative, ICU	All patients*	6†	Rel. tachycardia/hypotension‡	ST-segment changes§	Yes
	>80 yr	7	Rel. tachycardia/hypotension‡	ST-segment changes§	Yes
	CAD	8	Rel. tachycardia/hypotension‡	ST-segment changes§	Yes
	CVD	7	Rel. tachycardia/hypotension‡	ST-segment changes§	Yes
	Fever/hypermetabolism	7	Rel. tachycardia/hypotension‡	ST-segment changes§	Yes
Ward	All patients	6†	Rel. tachycardia/hypotension‡	Clinical signs¶	NA
	>80 yr	8	Rel. tachycardia/hypotension‡	Clinical signs¶	NA
	CAD	9	Rel. tachycardia/hypotension‡	Clinical signs¶	NA
	CVD	8	Rel. tachycardia/hypotension‡	Clinical signs¶	NA
	Fever/hypermetabolism	8	Rel. tachycardia/hypotension‡	Clinical signs¶	NA

NA, not applicable.

global and regional oxygen supply as indicated by signs of inadequate global and regional oxygenation. These physiological transfusion triggers based on the individual patient's characteristics make a thorough knowledge of transfusion physiology and clinical experience indispensable. However, numerical transfusion triggers may be helpful in certain situations such as when monitoring is inadequate or there is a lack of sufficiently experienced medical personnel.

Current evidence from studies of the influence of allogeneic blood transfusion on efficacy and clinical outcome is seriously hampered by the absence of a significant number of adequately powered RCTs. In addition, the only large RCT that compared a restrictive versus a liberal transfusion strategy, the TRICC trial, was done in ICU patients. There has been no sufficiently powered RCT in the perioperative setting. Therefore the findings from the frequently cited observational studies (ABC and CRIT study) and the TRICC trial can only be extrapolated with caution to perioperative transfusion decisions. Furthermore, 'hot topics' in transfusion medicine that have to be addressed by future large RCTs are the effect of different transfusion thresholds on morbidity and mortality, particularly in the perioperative setting and in CVD patients, the impact of RBC storage on transfusion efficacy and the role of leucoreduction.

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