Physiology, Benefits and Risks of Red Blood Cell Transfusion

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Introduction

Since Adams and Lundy recommended the "10/30 rule" as a guide for transfusion of red blood cells (RBC) in 1942 [1], understanding of the pathophysiology of anemia and insights into the risks of transfusion have, or should have, considerably changed transfusion policy. In addition, large trials have failed to show any benefit of transfusion with hemoglobin levels as low as 7 g/l for most patients, and for selected patient groups, transfusion might even worsen outcome. The pivotal study published by Hebert and his coworkers in 1999 is a landmark on the path to new standards of patient care [2]. Increasing costs and decreasing RBC availability will augment the pressure on physicians to follow more restrictive transfusion guidelines. This chapter gives an overview of the different elements which should result in a rational and balanced transfusion strategy.

Physiology of Oxygen Transport and Pathophysiology of Anemia

Oxygen Transport

Oxygen supply must match tissue oxygen needs to ensure aerobic cell respiration. Whole body oxygen delivery (DO_2) is the product of blood flow or cardiac output and arterial oxygen content (CaO_2):

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

Where DO_2 is expressed in ml/min, cardiac output in l/min and CaO_2 in ml/l.

CaO_2 is the sum of hemoglobin-bound and dissolved oxygen:

$$CaO_2 = (SaO_2 \times k_1 \times [Hb]) + (k_2 \times PaO_2)$$

where SaO_2 (%) is the arterial oxygen saturation, k_1 represents the oxygen-carrying capacity of hemoglobin which is 1.34 ml/g, [Hb] is the hemoglobin concentration (g/l), k_2 reflects the plasma oxygen dissolution coefficient at body temperature (0.23 ml/l/kPa) and PaO_2 equals the partial pressure of oxygen of arterial blood (kPa). The complete formula describing DO_2 thus reads as follows:

$$DO_2 = CO \times ((SaO_2 \times k_1 \times [Hb]) + (k_2 \times PaO_2))$$

Under physiologic conditions, DO_2 (800 to 1200 ml/min) exceeds oxygen consumption (VO_2) up to 4 times, resulting in an oxygen extraction ratio ($O_2ER = VO_2/DO_2$) of 20 to 30%. Consequently, even a marked isolated decrease in hemoglobin concentration will still result in a sufficient DO_2 to meet tissue oxygen requirements. However, below a critical hemoglobin concentration there will not only be a decrease in DO_2 but also in VO_2. This relationship of VO_2 and DO_2 is referred to as the concept of critical DO_2 (DO_2crit): above DO_2crit, tissue oxygenation is sufficient as represented by a constant VO_2 which is thus 'DO_2-independent'. In contrast, below DO_2crit body oxygen demands are no longer met resulting in a decrease of VO_2. This state is characterized by a 'VO_2/DO_2-dependency' and the development of tissue hypoxia [3].

Physiologic Adaptation to Normovolemic Anemia

In normovolemic anemia, several physiological mechanisms compensate for the decrease in hemoglobin concentration, in order to maintain DO_2 above DO_2crit. The key adaptation mechanisms to anemia are:

- an increase in cardiac output,
- redistribution of blood flow between organs, and
- an increase in O_2ER [4].

Cardiac output increases mainly through two mechanisms: reduced blood viscosity and increased sympathetic stimulation of the heart. The decrease in blood viscosity due to the lower hematocrit 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 (SVR) and afterload [5]. Increased sympathetic activity leads to an increase in myocardial contractility that contributes significantly to increased cardiac output [6]. An increase in the heart rate in response to increased sympathetic activity is only relevant in unmedicated humans [3, 7]. In contrast, in anesthetized humans, heart rate does not seem to respond to anemia [3, 7, 8]. The increase in cardiac output as a response to normovolemic anemia in anesthetized patients is therefore primarily due to an augmented stroke volume, and an increase in heart rate should be considered as a sign of hypovolemia.

Blood redistribution from non-vital to vital organs such as the heart and brain is mediated by the adrenergic system. This is especially important for the myocardium that has a high basal O_2ER with a relatively small oxygen extraction reserve. In contrast to the brain, which is able to significantly increase O_2ER, DO_2 to the heart is primarily increased by augmenting coronary blood flow. In addition, in response to the elevated blood flow to the microcirculation, the homogeneity of the capillary bed is augmented. This happens both with respect to changes over time (temporal heterogeneity) and to differences between vessels (spatial heterogeneity) as only about one third of capillaries is perfused under normal conditions. The resulting homogeneity leads to an increased O_2ER [4]. Finally, due to increased synthesis of 2,3-diphosphogylcerate (2,3-DPG) in red cells, the oxyhemoglobin dissociation curve shifts to the right thus allowing more hemoglobin-bound oxygen to be released at a given partial pressure of oxygen [5].

Tolerance to Anemia: How Low can You go?

In experimental settings, healthy volunteers have been shown to tolerate hemoglobin levels of 5 g/l under normovolemic conditions [9]. In a case report of an 84-year-old Jehovah's Witness patient, the hemoglobin concentration at which DO_2crit was reached (Hbcrit), was about 4 g/l. A review of the literature on Jehovah's Witness patients identified 134 medical and surgical patients with a hemoglobin concentration ≤8 g/l or a hematocrit ≤24% [10]. Among these 134 patients, 50 deaths were reported of which 23 were attributed exclusively or primarily to anemia. All these patients – with the exception of three patients with cardiac disease who died after cardiac surgery and two patients with missing laboratory data – died with a hemoglobin concentration ≤5 g/l or an equivalent hematocrit. Notably, this value was also found in 27 of the survivors. The effect of progressive anemia on morbidity and mortality in a surgical population has been described in a retrospective cohort study of 300 patients who refused blood transfusions for religious reasons, with a postoperative hemoglobin level of 8 g/l or less [11]. The odds ratio (OR), for mortality and morbidity, was 2.2 for each gram decrement in hemoglobin, but all patients in the group with a postoperative hemoglobin level of 7.1 to 8.0 g/l group survived. In the 6.1 to 7.0 g/l group 8.9% of patients died. Mortality increased steadily, reaching 100% in patients with 1.1 to 2.0 g/l of hemoglobin.

These findings further support the most recent recommendations that define a hemoglobin concentration ≤6 g/l as a transfusion trigger, which is quite close to the Hbcrit that can be presumed from the available literature [12]. Furthermore, in the range of 6 to 10 g/l, individual assessment of each patient's risk for complications of inadequate oxygenation is warranted. A number of clinical risk factors that may decrease a patient's tolerance to anemia and thus increase Hbcrit have been identified [13]. Patients with coronary artery disease may be particularly at risk as an adequate increase of the coronary blood flow in response to a decrease in hemoglobin concentration is not possible and myocardial ischemia may develop. In addition, impaired myocardial contractility may limit the compensatory increase in cardiac output. A retrospective cohort study in 1958 patients who declined blood transfusions due to religious reasons corroborated this hypothesis [14]. It was found that below a preoperative hemoglobin concentration of about 10 to 11 g/l the mortality increased in patients with and without cardiovascular disease, but more in those with cardiovascular disease. Conversely, the analysis of a subgroup of patients with cardiovascular disease in the TRICC trial (Transfusion Requirements in Critical Care) conducted by Hebert, showed no differences in mortality rate between a restrictive and a liberal transfusion strategy in patients with cardiovascular disease [15]. Although the authors were aware of the possible limitations of this subgroup analysis, they suggested a transfusion trigger of 7 g/l to be safe in critically ill patients with cardiovascular disease [15]. Possible exceptions were patients with acute myocardial infarction and unstable angina. Recent reviews on this topic have concluded that transfusion triggers for patients with cardiovascular disease should not differ substantially from patients without cardiovascular disease but may be mildly elevated [16, 17]. Nevertheless, in healthy patients, as in patients with concomitant diseases, RBC transfusion should be guided by clinical signs of inadequate oxygenation [12, 16]. In the case of patients with cardiovascular disease, new ST-segment depression >0.1 mV, new ST-segment elevations >0.2 mV, or new wall motion abnormalities in transesophageal echocardiography (TEE) may represent signs of inadequate oxygenation of the myocardium [16].

Rationale and Efficacy of RBC Transfusions: Why Transfuse?

Rationale of RBC Transfusion

The goal of RBC transfusion should be the increase in VO_2, thereby restoring adequate tissue oxygenation, or to alleviate signs of inadequate tissue oxygenation [18]. Increasing DO_2 without a concomitant increase in VO_2 would indicate the absence of VO_2/DO_2-dependency and thus any increase in DO_2 would be of questionable relevance [18]. Out of eighteen studies examining the effect of RBC transfusions on oxygenation parameters, 14 showed an increase in DO_2 associated with transfusion but in only 5 of them was this coupled to a parallel increase in VO_2 [19]. This lack of increase in VO_2 after RBC transfusion could be explained by the absence of an oxygen debt prior to infusion. Alternatively, dysfunction of stored RBC could be a reason for the lack of increase in VO_2 after RBC transfusion [18]. During storage, RBCs undergo different changes which are summarized under the term 'storage lesions' [20]. These include a decrease in 2,3-DPG, ATP depletion, and the release of pro-inflammatory substances. This results in a left shift of the oxyhemoglobin dissociation curve (i.e., increased oxygen affinity), impaired RBC deformability and inflammatory reactions in the transfusion recipient [20, 21]. The decrease in 2,3-DPG levels and RBC deformability, in particular, would imply decreased efficacy of 'old' RBC and thus no increase in VO_2 after transfusion. In addition, changes in nitric oxide (NO) biology cause a gradual depletion of NO in stored RBCs. NO is essential for oxygen exchange and the transfused RBCs may act as "NO-sinks" provoking vasoconstriction, platelet aggregation, and ineffective DO_2 [22].

How can we identify the patients who will increase VO_2 after RBC transfusion? Casutt and co-workers examined 67 cardiovascular surgery patients who were transfused with a total of 170 RBC transfusions [23]. Hemodynamic and oxygen consumption parameters were measured approximately 5 hours before and after transfusion. Pretransfusion hemoglobin, preoperative ejection fraction and age were found to be unrelated to individual responses in cardiac index (CI), DO_2 and VO_2 after RBC transfusion. In contrast, DO_2 and VO_2-related variables correlated well with and allowed better prediction of individual responses to RBC transfusions. In particular, a low VO_2 index correlated very well to an increase in VO_2 after transfusion. Similarly, a study evaluating whole-body O_2ER as a parameter for guiding transfusions [24] included 70 patients undergoing coronary artery bypass graft (CABG) surgery with a postoperative hematocrit $\leq 25\%$. O_2ER was monitored without influencing transfusion decisions. A retrospective analysis showed that if an $O_2ER \geq 45\%$ had been used as a transfusion trigger, it would have influenced transfusion therapy. Only 7 out of 41 transfused patients reached this transfusion trigger, as did 3 out of 35 patients who were not transfused. Thus, it was concluded that whole-body O_2ER may be a helpful parameter in a transfusion algorithm [24].

Efficacy of RBC Transfusion

It seems very hard to prove whether transfusion of RBC in patients with hemoglobin values above the critical level has any benefit at all. Moreover, more and more studies suggest that blood transfusion might do more harm than good in selected patient groups with hemoglobin values of more than 7 g/dl. The information emer-

ging from these data is often hard to interpret because of methodological differences and biases. For example, in a retrospective analysis of 1222 consecutive patients undergoing hepatectomy, perioperative blood transfusion was an independent risk factor for hospital morbidity and mortality in a multivariate risk analysis [25]. But, the advances in surgical technique, leading to an important reduction in blood loss and hence transfusion requirements, are likely to be the underlying cause for both the improved survival and the reduction in RBC transfusion. Various large observational studies have examined the effect of RBC transfusion on mortality and morbidity in intensive care settings with often contradictory results. The CRIT study (Anemia and blood transfusion in the critically ill – Current clinical practice in the United States) enrolled 4892 patients from August 2000 to April 2001 [26]; 44.1% of the patients were transfused with one or more RBC unit. The mean pre-transfusion hemoglobin was 8.6 ± 1.7 g/dl. The number of RBC units transfused was an independent risk factor for mortality and hospital length of stay (LOS). In addition, patients who were transfused experienced more complications. The ABC study (Anemia and blood transfusion in the critically ill), was performed in European intensive care units (ICUs) [27]. Similar to the CRIT study, 37.0% of the 3534 patients included (enrolment from November 15 to November 29, 1999) were transfused with mean pre-transfusion hemoglobin of 8.4 ± 1.7 g/dl. Mortality was higher for transfused patients compared to 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% vs. 17.1%, $p = 0.02$). The most recently conducted study, the SOAP study, enrolled 3147 patients between May 1 and May 15, 2002 [28]; 33% received RBC transfusion. Patients receiving transfusions were older and generally sicker, and 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 better survival in transfused patients.

To date, only one randomized controlled trial has sufficient power to evaluate the effect of transfusions on mortality and morbidity in the ICU. From 1994 to 1997, Hébert et al. enrolled 838 patients who were admitted to the ICU with an initial hemoglobin concentration of ≤ 9 g/dl [2]. The patients were randomized to either a restrictive transfusion strategy with a transfusion trigger of 7 g/dl (target hemoglobin 7 to 9 g/dl) or a liberal transfusion strategy with a transfusion trigger of 10 g/dl (target hemoglobin 10 to 12 g/dl). Thirty-day mortality was slightly lower in the restrictive transfusion group (18.7 vs. 23.3%), although statistical significance was not reached ($p = 0.11$). Even for patients with cardiovascular disease there seemed to be no benefit of transfusion if hemoglobin levels were 7 g/dl or more. However, subgroup analyses of patients less than 55 years of age or patients who where less acutely ill, as defined by an APACHE II score, showed significantly lower 30-day mortality in the restrictive transfusion group. As mentioned before, the authors state that patients with active coronary syndromes might be an exception, and that higher hemoglobin based transfusion triggers might be justified in this subgroup.

Initially, this view seemed to be confirmed by a report by Wu et al. [29] of a retrospective study on 78 974 patients of more than 65 years with acute coronary infarction. They categorized the patients according to hematocrit on admission and determined whether there was an association between the transfusion of RBCs and

30-day mortality. They found a beneficial effect of allogeneic blood transfusion if the hematocrit on admission was lower than 30%. On the contrary, if initial hematocrit was higher than 36%, transfusion was associated with increased mortality. This study, however, has an important bias in that patient characteristics and treatment varied significantly between patients with a low and patients with a high admission hematocrit [16]. A very recent report on the relationship of blood transfusion and outcome in patients with acute coronary syndromes (ACS), however, reaches the opposite conclusion. Rao and co-workers pooled the study populations of three large international trials (GUSTO IIb, PURSUIT, and PARAGON b) on patients presenting with ACS and assessed the association of RBC transfusion and outcome [22]. The data of 24 112 patients were examined on the propensity to bleed or receive transfusion and on the association between transfusion and 30-day death. After adjustment for baseline characteristics, blood transfusion was associated with a hazard ratio for death of 3.54 and after adjustment for baseline characteristics, bleeding, transfusion propensity, and nadir hematocrit blood transfusion was still independently associated with a hazard ratio for death of 3.94. There was no significant association between transfusion and 30-day mortality in patients with a nadir hematocrit of 25% or less, but at a nadir hematocrit above 25% RBC transfusion was linked to a higher 30-day mortality. Compared to the trial conducted by Wu, who used the hematocrit value on admission only, Rao's team based their comparison on the nadir hematocrits measured during hospitalization. Further, patients under 65 years of age and patients undergoing heart surgery were excluded in the study by Wu [29], whereas all patients regardless of age, bleeding events, or procedures were included by Rao et al. They concluded that, in the setting of ACS, blood transfusion was associated with an increased risk of 30-day mortality for patients with a hematoctrit above 25%, even after adjustment for patient characteristics, baseline and nadir hematocrit, bleeding, and in-hospital procedures.

How should we interpret the results of these randomized controlled and observational trials? The validity of the observational studies is not clear because sicker patients are more likely to be transfused [30]. Although retrospective propensity analysis tries to control for potentially confounding factors, this adjustment can only be done for factors recorded. It is thus possible that unmeasured confounders bias the results. Consequently, we can only draw conclusions about statistical associations between factors and not about causality.

But what explains the overtly contradicting results between some of these trials? The GUSTO IIb, PURSUIT, and PARAGON b trials were all conducted between July 1994 and January 1996. And it was not until 1998 that the Blood Product Advising Committee of the US Food and Drug Administration voted for universal leukoreduction [31]. At the time of inclusion of the patients for the ABC study, universal leukoreduction had not been implemented in Germany, Holland, Norway, or Finland, accounting for about one third of the 3534 patients, while other participating countries were just completing it [32]. By the time the SOAP-study ran, leukoreduction was much more common. Universal leukoreduction is the subject of substantial debate. One unit of blood (approximately 500 ml) contains about 2 billion white blood cells (WBC). After processing, 90% of these are found in the RBC aliquot, primarily as granulocytes [31]. Leukoreduction aims to reduce this amount of WBC by 99.995%, leaving 5000 residual leukocytes. Leukocytes present in RBCs are held responsible for transfusion-associated immunomodulation (TRIM), febrile transfusion reactions, and transmission of intracellular pathogens such as cytome-

galovirus (CMV), human T-cell lymphotropic virus (HTLV)-I and HTLV-II, Epstein-Barr virus (EBV), Herpes viruses, parasites, and prions [31]. A before-and-after cohort study in Canada found a reduction in mortality, post-transfusion fevers and antibiotic use after implementation of a universal leukoreduction program [33]. A recent prospective cohort-controlled study observed a decrease in hospital LOS in open-heart surgery with leukoreduced blood transfusions [34]. In contrast, a before-and-after study in the UK observed no impact on hospital LOS and postoperative infection in orthopedic and cardiac surgery [35].

Finally, the age of RBC units may be another important factor influencing the efficacy of RBC transfusion as outlined above. Although highly controversial, this parameter might explain some of the observed differences between the trials [20].

Transfusion-related risks. Why not Transfuse?

Transfusion-related risks can be divided into transfusion-transmissible infections, immunologic risks, and mistransfusion.

Infectious Risks

RBC transfusions in Western countries have probably never been safer than today with respect to transfusion-transmissible viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) [36]. The estimated risks of infection have dramatically decreased over recent years because increased test sensitivity has reduced infectious window periods [37]. Estimates of current risk are shown in Table 1.

In contrast to Western countries, viral and parasitic transfusion-transmissible infections are a major problem in countries with a low human development index (HDI, an index based on life expectancy, literacy, enrolment into scholarly education, and per capita income) (Table 1). A high seroprevalence of these diseases in the general population of these countries, poorly organized blood donation systems, and poor sensitivity of pathogen testing are important factors [36]. The future transfusion practice in low HDI countries will strongly depend on international investment to guarantee an appropriate transfusion safety [38].

Compared to viral transfusion-transmissible infections, there is currently much more concern about transfusion-transmitted bacterial infections and post-transfusion sepsis [39] in high HDI (Western) countries. Because of the high platelet storage temperature of 20–24°C, which favors bacterial growth, contamination of platelets is more common than contamination of RBC units. Best risk estimates of transfusion-transmitted bacterial infections from a Canadian study gave values in the range of about 1:2000 to 1:8000 (13 to 44 per 100 000) for platelet pools and 1:28 000 to 1:143 000 (0.7 to 3.6 per 100 000) for transfused RBC units [40]. Notably, when comparing the incidence of transfusion-transmitted bacterial infections from different studies, the different diagnostic criteria of transfusion-transmitted bacterial infections should be considered [40].

Recently, the first possible cases of transfusion-transmitted variant Creutzfeld-Jakob disease (vCJD) have been reported [41, 42]. The probability that the first case of vCJD was not due to transfusion-transmitted vCJD ranged between 1:15 000 to 1:30 000. The hypothesized incubation period of transfusion-transmitted vCJD was

Table 1. Transfusion-associated risks (modified from [35])

Type of Risk Infections	Estimate of current risk (infection rate per unit)	
	High HDI countries	Low HDI countries
INFECTION		
Viruses		
▪ Human immunodeficiency virus (HIV)	1:1 468 000–1:4 700 000	1:50–1:2578
▪ Hepatitis B virus (HBV)	1:31 000–1:205 000	1:74–1:1000
▪ Hepatitis C virus (HCV)	1:1 935 000–1:3 100 000	1:2578
Bacteria (contamination)	1:2 000–1:8 000 (platelet pools)/ 1:28 000–1:143 000 (red cells)	?
Parasites		
▪ Malaria	1:4 000 000	up to 1:3
Prions		
▪ Variant Creutzfeld-Jacob disease	first two possible transmissions described	?
IMMUNOLOGIC REACTIONS		
Hemolytic Transfusion Reactions		
▪ Acute Hemolytic	1:13 000	?
▪ Delayed Hemolytic	1:9 000	?
▪ Alloimmunization	1:1 600	?
▪ Autoimmunization	? (recently identified as risk)	?
▪ Immunosuppression	1:1	?
▪ Transfusion-related acute lung injury	1:70 000	?
▪ Mistransfusion	1:14 000–1:18 000	?

6.5 years [41]. Britain's second transfusion-transmitted case of vCJD may have been caused by a blood transfusion dating back to 1999 [42]. This patient died of causes unrelated to vCJD. Identical to the first case, this patient was the recipient of non-leukodepleted 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 tonsils which suggests an intravenous rather than an oral route of transmission [42]. An incubation period of 6.5 years in asymptomatic vCJD patients could represent a significant source of iatrogenic infection by blood donation or by contamination of surgical instruments [42]. This led the UK government to take precautionary measures, deferring blood from an important part of the donor pool (see further). Interestingly, it has been shown that leukoreduction is efficacious in reducing but fails to eliminate white-cell-associated transmission of spongiform encephalopathies [43]. In addition, some infectivity of transmissible spongiform encephalopathies is assumed to be plasma-associated [43]. Therefore, the policy of leukoreduction aimed at reducing transmissible spongiform encephalopathy infectivity may require re-evaluation.

Immunologic Risks

In contrast to low HDI countries that are very concerned with transfusion-transmissible infections, immunologic transfusion reactions are generally more frequently encountered in high HDI countries [36] (Table 1).

As mentioned, RBC transfusions seem to have an immunomodulatory effect, the causes of which remain unclear. Although several studies have suggested that WBCs cause immunomodulation, the blood components that may mediate this effect are still not defined. It goes beyond the scope of this review to discuss all other immunological risks in detail, the reader is therefore referred to a very comprehensive review on risks associated with RBC transfusions in Canada [40]. However, transfusion related acute lung injury (TRALI) is a controversial issue that should be mentioned. Estimates of the incidence vary from 0.2 per 100 000 [44] to 1 per 5 000 RBC units transfused [45]. These discrepancies are thought to be caused by underreporting [40, 46] due to a lack of awareness or misdiagnosis. The symptoms and signs of TRALI do resemble other conditions associated with transfusion and volume overload such as adult respiratory distress syndrome (ARDS) or congestive heart failure (CHF). Therefore, standardized criteria for the definition and diagnosis of TRALI are needed to calculate the incidence and allow for comparison between hospitals and transfusion policies [46].

Mistransfusion

Mistransfusion is associated with significant morbidity and mortality [47] and is unfortunately estimated to occur in one of 14 000–18 000 transfusions. It represents the transfusion hazard with the highest incidence in high HDI countries [37, 40, 47].

Societal Cost and Donor Selection

The societal cost for one unit of allogeneic RBCs transfused to in-patients cared for in emergency departments, ICUs, general medicine wards, and operating rooms in Canada was calculated to be US$ 264.81 [48]. The calculation comprised the costs for collection of blood (including the donor's cost of time) production, distribution, delivery, and administration of blood products, and the costs for transfusion reaction management. Compared to 1995, when the cost of a unit of RBC was US$ 157.17, this is a nearly two-fold increase. A large proportion of this increase is due to the implementation of nucleic acid testing (NAT) for HCV and HIV I/II, universal leukoreduction, other quality-assurance programs, and associated labor- and non-labor related costs. A cost simulation exercise showed that the cost might increase to US$ 317.77 assuming that the cost of hemovigilance, new quality tests, etc. would increase the mean cost by 20%. New tests for vCJD, West Nile Virus, microbial infections, and inactivation of pathogens will further increase production related costs.

Finally, these newly discovered transfusion transmissible pathogens are not only responsible for a probable increase in cost, but have already led to a dramatic decrease in the number of potential donors. In 1997, the concern about potential transmission of vCJD led to three blood withdrawals of products linked to vCJD donors. In 1998, the UK decided to import all their plasma requirements and leu-

koreduce their blood, since the prion seemed to be primarily located in WBCs. Soon after, Canada and the US decided to defer all blood products from individuals who had lived in the UK for 6 months between 1980 and 1996. France introduced a deferral policy for all donors who had lived in the UK for one year and implemented universal leukoreduction. In April 2004, the UK decided to defer all donations from individuals who have been transfused since 1980 [49]. The ban on these blood products reduced the number of donors in the UK by 3.3% [50]. And finally, when confirming the second case of transfusion transmission of vCJD in July 2004, the UK Committee on the Microbiological Safety of Blood and Tissue advised to extend the ban to donors who are unsure whether they have had a blood transfusion and to apheresis donors who have previously had a blood transfusion. The impact of the extended ban, which will become effective from April 2005, remains to be seen.

Conclusion

The transfusion of RBCs has been used for decades to improve the oxygen transport capacity and oxygen consumption related parameters of anemic patients. New insights into the pathophysiology of allogeneic blood transfusions question the capacity of stored RBC to improve these factors in most patients. Although class A evidence is lacking, most survey's have found no benefit whatsoever of RBC transfusions in patients with hemoglobin levels above 7 g/dl and, for selected patient groups, it could even compromise outcome. It seems that the WBCs present in units of packed RBCs are, at least partially, responsible for some of the complications associated with transfusion. Generalized application of leukoreduction might shift the balance in favor of transfusion, but it is too early to draw any definitive conclusions on this subject. Future trials will provide some of the answers and doubtless raise new questions. Meanwhile, increasing costs and shrinking pools of donors are a supplemental driving force to rationalize transfusion practice.

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The Microvasculature