

CLINICAL ANAESTHESIOLOGY

The *Best Practice & Research* series aims to provide a topical serial publication describing and integrating the results from the latest original research articles into practical, evidence-based review articles. These articles seek to address the key clinical issues of diagnosis, treatment and patient management. Each issue follows a problem-orientated approach which focuses on the key questions to be addressed, clearly defining what is known and not known. Management is described in practical terms so that it can be applied to the individual patient. The serial is aimed at the physician in both practice and training.

Best Practice & Research Clinical Anaesthesiology is abstracted and indexed in the following sources: Index Medicus, Medline, PubMed, Current Contents/Clinical Medicine, Current Contents/Life Sciences, Science Citation Index, SciSearch, Research Alert and EMBASE/Excerpta Medica.

Editor-in-Chief

H. Van Aken
Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin
Universität Münster
Albert Schweitzer Str. 33
D-48129 Münster
Germany

Editorial Board

I. Acalovschi, Romania
A. Aitkenhead, UK
J. Andres, Poland
D. C. H. Cheng, Canada
M. E. Durieux, The Netherlands
A. W. Gelb, USA
S. Gelman, USA

H. Kehlet, Denmark
K. Leslie, Australia
P. Pelosi, Italy
J. Scholz, Germany
A. Schug, Australia
K. Shingu, Japan
D. Spahn, Switzerland

Index

- acute lung injury, 183
- alternatives, 221
- anaemia, 163
- anaemia tolerance, 221
- anti-platelet therapy, 241
- aortic stenosis, 163
- artificial O₂ carriers, 221

- blood, 221, 272
- blood products, 257, 272
- blood substitutes, 221
- blood transfusion, 195
- blood transfusion/adverse effects, 183

- cardio-vascular risk, 163
- cell salvage, 221
- central venous O₂ saturation (ScvO₂), 173
- circulation, 163
- coagulopathy, 257
- coronary stent thrombosis, 241

- donation, 221

- economics, 272
- electroencephalographic P300 latency, 173

- haemodilution, 221
- haemoglobin, 163
- haemorrhage, 257
- haemostasis, 257

- lactate, 173
- leucoreduction, 209

- microcirculation, 195, 209
- mitral insufficiency, 163

- non-cardiac surgery, 241
- normovolaemic haemodilution, 163

- oxygen (O₂) transport (TO₂), 173
- oxygen delivery, 209
- oxygen uptake, 209

- pulmonary edema, 183

- red blood cell, 195
- regional tissue oxygenation, 173

- storage, 195
- storage lesion, 209
- surgical haemorrhage, 241

- tissue oxygenation, 195
- transfusion, 221, 272
- transfusion triggers, 195
- trauma, 257

- venous O₂ saturation (SvO₂), 173



ELSEVIER

Best Practice & Research Clinical Anaesthesiology
Vol. 21, No. 2, p. 161, 2007
doi:10.1016/j.bpa.2007.02.005
available online at <http://www.sciencedirect.com>



Preface

Blood transfusions in 2007: Risks, alternatives and indications

Avoiding allogeneic blood transfusions also in 2007 remains an important goal in the perioperative treatment since blood transfusions are still associated with risk and a limited efficacy. To reach this goal, we need a detailed knowledge of the physiology of oxygen transport, the risks involved and the alternatives available. From the knowledge of the physiology of oxygen transport physiologic transfusion triggers may be deduced.

Special considerations deserve the use of blood and blood products in trauma and the use of anti-platelet drugs perioperatively. Last but not least the costs of blood transfusions are perceived as high but may remain significantly underestimated.

All the above aspects are covered in this issue of "Best Practice & Clinical Anaesthesiology" and will hopefully help the clinician to better treat patients.

Donat R. Spahn
*Institute of Anaesthesiology,
University Hospital Zürich,
CH-8091 Zürich, Switzerland*
E-mail address: donat.spahn@usz.ch



I

Allogeneic red blood cell transfusion: Physiology of oxygen transport

Caveh Madjdpour MD

Resident

Donat R. Spahn* MD, FRCA

Professor and Chairman

Department of Anaesthesiology, University Hospital Zurich, CH – 8091 Zurich, Switzerland

Allogeneic red blood cell (RBC) transfusions have been shown to be associated with considerable risks. While their efficiency in many clinical situations has not been proven, the number of studies finding adverse outcomes in terms of morbidity (e.g. postoperative infections) and mortality continues to rise. In view of these facts, physicians involved in transfusion medicine have to be as restrictive as possible with RBC transfusions. Only a thorough knowledge of the physiology and pathophysiology of oxygen transport can be a solid base for meaningful transfusion decisions. Therefore, the goal of this article is to review the basics of oxygen transport and normovolaemic anaemia.

Key words: anaemia; normovolaemic haemodilution; haemoglobin; circulation; cardio-vascular risk; aortic stenosis; mitral insufficiency.

INTRODUCTION: RISKS OF RED BLOOD CELL TRANSFUSION

While there is still an astonishing lack of evidence for the efficacy of red blood cell (RBC) transfusions, the number of well-conducted studies establishing a link between RBC transfusion and poor outcome is large and still continues to increase. Numerous randomized controlled trials (RCTs) and observational studies have examined the outcomes after allogeneic RBC transfusions. The Transfusion Requirements in Critical Care (TRICC) Trial investigated the effect of a restrictive transfusion strategy with a transfusion threshold of 7 g/dl (target haemoglobin 7 to 9 g/dl) vs. a liberal transfusion strategy with a transfusion trigger of 10 g/dl (target haemoglobin 10 to 12 g/dl) on outcome in ICU patients. 30-day mortality was comparable between the two groups,

* Corresponding author. Tel.: +41 44 255 26 95; Fax: +41 44 255 44 09.
E-mail address: donat.spahn@usz.ch (D.R. Spahn).

indicating that a liberal transfusion strategy did not offer an advantage.¹ Interestingly, subgroup analyses of patients that/who were less severely ill (APACHE II score < 20) and patients that/who were less than 55 years of age showed a significantly lower 30-day mortality in the restrictive transfusion group.¹ The favourable outcome refers to TWO subgroups of patients (less severely ill patients as defined by an APACHE II score < 20 and younger patients as defined by an age < 55). Two large observational studies, the ABC (Anemia and blood transfusion in the critically ill) and the CRIT (Anaemia and blood transfusion in the critically ill – Current clinical practice in the United States) study noted associations between transfusion and mortality.^{2,3} The ABC study performed in European intensive care units found a significantly higher mortality in transfused vs. non-transfused patients with similar organ dysfunction. Even after matching patients for being transfused, 28-day mortality was significantly higher in transfused vs. non-transfused patients (22.7% vs. 17.1%, $p = 0.02$).² Similarly the US CRIT study identified the number of RBC units transfused as an independent risk factor for mortality and length of hospital stay.³

In view of the results of these landmark studies and other trials on transfusion and outcome, the harmful effects of transfusions under certain circumstances are undisputable. Therefore, the reluctance to consider RBC transfusions as potentially harmful and avoidable interventions that is often encountered in daily practice among physicians involved in perioperative and intensive care medicine is difficult to understand. All the more it is important to have a good knowledge of the rationale upon which RBC transfusions are based upon, that is oxygen transport.

OXYGEN TRANSPORT: BASIC PRINCIPLES

The rationale of a RBC transfusion is improvement of oxygen transport and ultimately tissue oxygenation. Therefore, thorough knowledge of the physiology of oxygen transport is a prerequisite when transfusing patients.⁴ Aerobic metabolism depends on continuous oxygen delivery (DO_2) to the cells in order to meet their metabolic requirements. An inadequate oxygen supply may lead to tissue hypoxia resulting in anaerobic metabolism and the production of lactate.

There are two important processes involved in oxygen transport: convection and diffusion. Oxygen in the inspired gas is transported by convective down to the alveoli, diffuses across the alveolo-capillary barrier, binds to haemoglobin and is transported – again by convection – to the microvascular network where it diffuses across the capillaries to the cells and finally into the mitochondria.

RED BLOOD CELL TRANSFUSION AND OXYGEN TRANSPORT

Global DO_2 is determined by cardiac output (CO) and arterial oxygen content (CaO_2):

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$

Where DO_2 is in ml/min, CO in l/min and CaO_2 in ml/l.

CaO_2 is the sum of the haemoglobin-bound form of oxygen and physically dissolved oxygen in plasma:

$$\text{CaO}_2 = (\text{SaO}_2 \times 1.34 \times [\text{Hb}]) + (0.03 \times \text{PaO}_2)$$

Where the haemoglobin-bound oxygen is the product of the arterial oxygen saturation (SaO_2 , in %), the oxygen-carrying capacity of haemoglobin (1.34, in ml/g) and the haemoglobin concentration ($[Hb]$, in g/l) and dissolved oxygen is the product of the plasma oxygen dissolution coefficient at body temperature (0.03, in ml/(l \times mmHg)) and the partial pressure of oxygen in arterial blood (PaO_2 , in mmHg).

Global oxygen consumption (VO_2) which describes the amount of oxygen consumed by the whole body per minute ranges under physiological conditions in a normal adult from 200 to 300 ml/min whereas DO_2 ranges from 800 to 1200 ml/min. The relationship VO_2/DO_2 defines the oxygen extraction ratio (O_2ER) which is thus in the range of 20 to 30%. A normal VO_2/DO_2 -relationship is illustrated in Figure 1. It can be deduced from this graph that even a marked decrease in DO_2 is tolerated with respect to VO_2 which is held constant and thus “ DO_2 -independent”. This situation may occur e.g. in acute normovolaemic anaemia, where CaO_2 is reduced by the fall in haemoglobin concentration. However, beyond a critical value of DO_2 which is referred to as critical DO_2 ($DO_{2\ CRIT}$), VO_2 starts to decrease and becomes thus “ DO_2 -dependent” and tissue hypoxia develops.⁵

OXYGEN TRANSPORT BY DIFFUSION

Oxygen diffusion from the alveoli to the pulmonary capillaries or from the capillary network into the tissues can be described by Fick’s first law of diffusion:

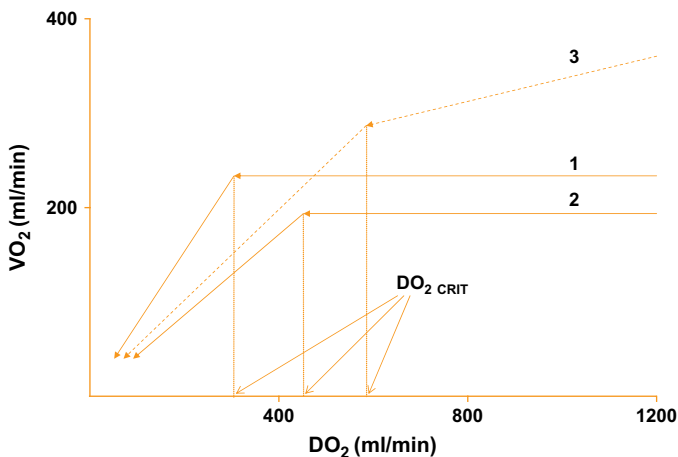


Figure 1. $VO_2 - DO_2$ relationship. Three different conditions are shown: individuals 1 and 2 differ in their metabolic demand, i.e. oxygen consumption (VO_2) which is held constant despite a decrease (arrowheads) in oxygen supply (DO_2). At a critical threshold of DO_2 ($DO_{2\ CRIT}$) which is reached sooner in individual 2 than in individual 1, VO_2 begins to fall rapidly. Individual 3 represents a particular condition: above $DO_{2\ CRIT}$, $VO_2 - DO_2$ relationship does not plateau as under physiologic conditions. In contrast, VO_2 continues to increase with increasing DO_2 even in a range of DO_2 that would be largely sufficient to meet metabolic demands under normal conditions and demonstrates therefore a “supply-dependency” indicating an oxygen debt. This situation may be found in critical illness such as sepsis.

$$\text{O}_2 \text{ rate of diffusion} = [K \times A \times \Delta P]/D$$

Where K is the diffusion coefficient of oxygen within the medium, A the surface area for diffusion, ΔP the pressure gradient across the diffusion barrier and D the distance over which diffusion occurs.

When applying Fick's equation to the diffusion process of oxygen from the capillaries to the mitochondria, ΔP represents the difference between the mean capillary oxygen partial pressure (PO_2) and the PO_2 near the mitochondria, while A and K characterize the capillary network with respect to its surface and capillary density. Accordingly, an increased PaO_2 enhances oxygen diffusion from the blood into the tissue by increasing the PO_2 pressure gradient. It may be argued that physically dissolved oxygen contributes little to CaO_2 and accordingly to DO_2 and that increasing PaO_2 above a threshold of about 70 mmHg therefore offers little extra benefit since over 90% of haemoglobin is already saturated with oxygen at this point of the oxyhaemoglobin dissociation curve (Figure 2). While the latter part of this statement concerning haemoglobin saturation is correct, the former one disregards the changes in blood composition present in case of acute normovolaemic anaemia. With decreasing haemoglobin values in acute normovolaemic anaemia the plasma compartment is significantly increasing and represents therefore a quantitatively important reservoir for physically dissolved oxygen. It has been demonstrated in animal experiments that physically dissolved oxygen can make up to 47% of VO_2 at a haemoglobin of 7 g/dl⁶ and 74% of VO_2 when hyperoxic ventilation (100% O_2) is applied in profound normovolaemic anaemia (haemoglobin of 3 g/dl).⁷ Already at 60% O_2 ventilation the critical haemoglobin could be lowered from 2.4 g/dl at 21% O_2 ventilation to 1.5 g/dl.⁸ At the critical haemoglobin of 1.5 g/dl 53% of the VO_2 was from physically dissolved oxygen. This finding is particularly important because long term ventilation with 60% O_2 is less

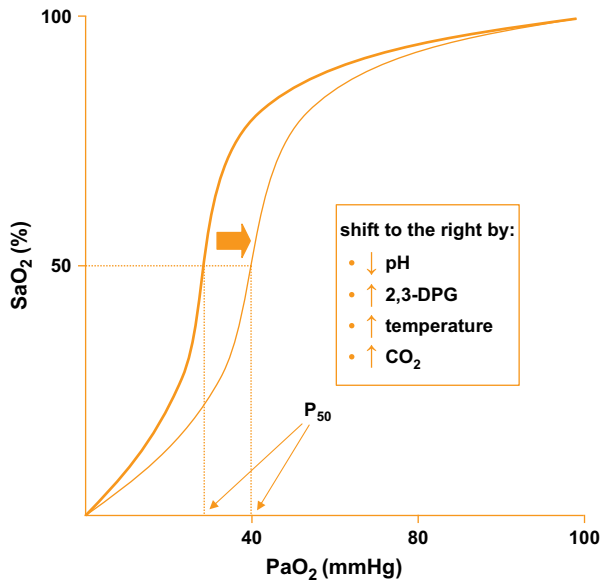


Figure 2. Oxyhaemoglobin dissociation curve. Changes in parameters leading to a rightwards shift are given (box). P50 = Oxygen tension at which haemoglobin is 50% saturated. 2,3-DPG = 2,3-diphosphoglycerate.

prone to be associated with O_2 toxicity than a ventilation with 100% O_2 and thus practically more feasible.⁹

Furthermore, Meier and co-workers have shown that hyperoxic ventilation significantly increases survival after acute normovolaemic haemodilution to individual critical haemoglobin values (Hb_{CRIT}). Ventilation with 100% oxygen resulted in a 6-hour mortality of 14% while all animals that were ventilated with room air (21% oxygen) died with 6 hours after Hb_{CRIT} had been reached.¹⁰ In addition to these animal studies, the beneficial effects of hyperoxic ventilation during normovolaemic anaemia have also been found in humans. In a recent study in patients after coronary artery bypass graft (CABG) surgery (haemoglobin 8.1–8.2 g/dl), ventilation with 100% oxygen resulted in an increase of DO_2 and skeletal muscle PO_2 but not in VO_2 .¹¹ However, similarly to the 47% contribution to VO_2 found in the animal study by Meier et al¹⁰, hyperoxic ventilation in normovolaemic anaemia does not only seem to result in convective transport of physically dissolved plasma, but also to increase the PO_2 pressure gradient between blood and tissue which facilitates oxygen diffusion and tissue oxygenation. Weiskopf and co-workers have investigated the effect of a marked increase in PaO_2 on haemodilution-induced deficits of cognitive function and memory in healthy volunteers.¹² Haemoglobin values decreased from 12.7 g/dl before haemodilution to 5.7 g/dl after haemodilution. Tests for cognitive function and delayed memory showed a significant impairment at these anaemic haemoglobin levels. These deficits were completely reversed by breathing oxygen which increased PaO_2 to approximately 400 mmHg.¹² Accordingly, this study convincingly demonstrated that an acute anaemia-induced oxygen supply-demand mismatch of the brain causing very subtle neurological deficits can be compensated by a massive increase of physically dissolved oxygen.

COMPENSATORY MECHANISMS IN RESPONSE TO ACUTE NORMOVOLAEMIC ANAEMIA

The primary goal in case of acute blood is to restore normovolaemia with crystalloids and colloids. Therefore we will premise normovolaemic anaemia when discussing physiologic alterations in response to acute anaemia.

Changes in blood flow represent a central mechanism that underlies a number of compensatory mechanisms keeping DO_2 above $DO_{2 CRIT}$.¹³ First, blood flow is augmented at the level of the central circulation by an increased cardiac output (CO). This is accomplished by a decrease in blood viscosity on one hand and an increase in sympathetic stimulation of the heart on the other hand.¹⁴ Decreased blood viscosity is due to the diminished number of RBC's and the reduction in haematocrit. This results in an increase in left ventricular performance by two mechanisms: an increased venous return and consequently an increased preload (Frank-Starling mechanism) and a decreased systemic vascular resistance and thus a decreased afterload.⁴

In anesthetized humans increased sympathetic activity leads to increased CO exclusively by increased myocardial contractility but not by an increase in heart rate.^{5,15,16} Therefore, in contrast to awake humans, any increase in heart rate anesthetized anaemic patients has primarily to be considered as a sign of hypovolaemia. In this regard it is important to note that chronic β -adrenergic blockade does not impair the central haemodynamic adaptation to mild normovolaemic haemodilution. Chronically β -blocked and non- β -blocked patients undergoing CABG surgery have been prospectively studied during preoperative acute normovolaemic haemodilution to haemoglobin

levels of roughly 10 g/dl.¹⁷ Both patient groups compensated well for the acute decrease in CaO_2 with VO_2 remaining unchanged in non- β -blocked patients and being slightly increased in β -blocked patients. However, there was an interesting difference in the compensatory mechanisms: while β -blocked patients showed an increase in cardiac index and oxygen extraction, non- β -blocked patients responded only with an increase in oxygen extraction. The authors hypothesized that this may be due to an up-regulation of β -adrenergic receptors during chronic β -blockade resulting in a greater increase of cardiac index in response to haemodilution-induced endogenous catecholamine secretion compared to non- β -blocked patients.¹⁷ Therefore, it would be interesting to investigate the effect of short-term perioperative β -blockade on cardiac output in response to acute normovolaemic haemodilution in humans since perioperative β -blockade has been shown to decrease morbidity and mortality in CAD patients and is therefore commonly applied.¹⁸ Second, regional redistribution of blood flow from non-vital to vital organs takes place. This redistribution occurs mainly in favours of heart and brain. This is particularly important for the myocardium that has an almost maximal O_2ER under physiologic conditions. Thus, increased myocardial oxygen requirements have to be met by an increase in DO_2 via an increase in coronary blood flow which enables the heart to maintain the macrocirculatory response to normovolaemic anaemia. However, an increased blood flow itself to the tissues does not necessarily result in an adequate DO_2 . Microvascular blood flow exhibits a considerable spatial heterogeneity with wide distributions of capillary haematocrit and RBC flow rates. Therefore, as a third compensatory mechanism, blood flow homogenization in the microcirculation resulting in an increase in the O_2ER is an important mechanism in the maintenance of an adequate tissue oxygenation.¹³ In addition to these blood flow alterations, increased RBC 2,3-diphosphoglycerate (2,3-DPG) levels lead to a decrease in the affinity of haemoglobin for oxygen with a shift of the oxyhaemoglobin dissociation curve to the right resulting in a facilitated release of haemoglobin-bound oxygen⁴ (Figure 2).

ADAPTATION TO NORMOVOLAEMIC ANAEMIA: PATIENTS AT RISK

The outlined compensatory mechanisms in response to acute normovolaemic anaemia can be impaired or $\text{DO}_2\text{ CRIT}$ – either systemic or organ specific – may be reached sooner under certain pathophysiological conditions, respectively.

Coronary artery disease

Patients with coronary artery disease (CAD) may be at particular risk to develop myocardial ischemia in case of an acute drop in CaO_2 caused by acute normovolaemic anaemia. This is mainly due to two reasons: first, the compensatory increase in coronary blood flow is limited by the fixed coronary stenosis. Second, the heart has already under physiologic conditions a relatively high O_2ER and therefore a limited capacity to increase O_2ER further. Thus, myocardial $\text{DO}_2\text{ CRIT}$ is reached sooner in these patients with ongoing haemodilution compared to patients without CAD.

It has been shown in patients with CAD scheduled for CABG surgery that haemodilution from 12.6 ± 0.2 g/dl to 9.9 ± 0.2 g/dl is well tolerated.¹⁹ The patients in this prospective, randomized study were able to increase both O_2ER and cardiac index in response to the acute decrease in CaO_2 . There were neither any signs of myocardial ischemia in the ECG nor any hints for cardiac dysfunction when systemic and pulmonary haemodynamic parameters were measured.¹⁹ These results were confirmed

recently in a similar study in CAD patients who were haemodiluted from 13.9 ± 1.3 g/dl to 9.3 ± 1.0 g/dl.²⁰ In addition to the absence of ECG abnormalities and haemodynamic instability, transoesophageal echocardiography did not exhibit any compromise in left ventricular systolic and diastolic function.²⁰ In addition, preoperative haemodilution resulted in less postoperative troponin release, a reduced need for inotropic support and fewer postoperative supra-ventricular arrhythmias.²¹ Thus, moderate haemodilution to haemoglobin levels of 8–9 g/dl seems to be safe in CAD patients and may even result in an outcome benefit.

Valvular heart disease

Acute normovolaemic haemodilution from 13.4 ± 0.7 g/dl to 9.1 ± 0.9 g/dl has recently been performed in patients with severe aortic stenosis (valve area of 0.6 ± 0.1 cm²).²² Preload indexes and cardiac output increased as expected. However the compensatory increase in left-ventricular stroke volume was limited due to loss of kinetic energy at the obstructed valve. Therefore, in case of severe aortic stenosis, haemodilution to values lower than 9 g/dl may be performed with caution. Haemodilution to haemoglobin values of 10 g/dL is well tolerated in patients with mitral valve insufficiency, even when atrial fibrillation is present.²³

It needs to be stressed that up to now, no studies have been performed on the safety of haemodilution in patients with other valvulopathies such as aortic insufficiency or mitral stenosis.

Impaired cardiac contractility

Significantly impaired cardiac contractility may limit the compensatory increase in response to acute normovolaemic anaemia. However, preoperative left-ventricular ejection fraction (LV EF) in the range of 26 to 83% has been shown not to influence the compensatory increase after haemodilution from 12.6 ± 0.2 g/dl to 9.9 ± 0.2 g/dl.¹⁹ Nevertheless, the number of patients with a LV EF below 35% was small and the results of this study may not be applied to all patients with severely impaired LV EF.

RBC TRANSFUSIONS AND OXYGEN KINETICS

Most physicians would agree that the ultimate goal of allogeneic RBC transfusions consists in increasing DO_2 in order to increase tissue oxygenation. However, numerous studies consistently failed to show an increase of tissue oxygen utilization as measured by VO_2 . Hébert and colleagues identified eighteen studies studying the effect of RBC transfusions on parameters including DO_2 and VO_2 . Of the fourteen studies that detected an increase in global DO_2 , only five detected an increase in global VO_2 .²⁴ A recent prospective randomized study in patients evaluated the effect of transfusion of 1 or 2 RBC units or ventilation with 100% oxygen on systemic oxygenation parameters in moderately anaemic patients (haemoglobin 8.1–8.2 g/dl) after primary CABG surgery.¹¹ Again, systemic VO_2 did not increase in the transfusion group. Only DO_2 increased as in the group that was ventilated with 100% oxygen. One reason for the lack of increase of VO_2 in all these studies might be the absence of a DO_2 -dependency of VO_2 prior to the transfusion. In the range of DO_2 -independency VO_2 is held constant by the compensatory mechanisms as discussed above. Therefore, from a physiological point of view, RBC transfusions in these situations are of questionable benefit in terms of oxygen kinetics.

OXYGEN TRANSPORT AND VISCOSITY

A recent animal study investigated the influence of blood viscosity on microvascular conditions in case of extreme haemodilution.²⁵ Haemoglobin was decreased by step-wise haemodilution to a haematocrit (Hct) of 18% and 11%. In addition, by exchange transfusion with RBCs containing methaemoglobin, a group with a haematocrit of 18% but an effective oxygen-carrying capacity of only about 11% Hct was created. Interestingly, microvascular perfusion and systemic conditions (e.g. mean arterial pressure) were significantly better in group with methemoglobin-containing RBCs compared with the 11% Hct group which was attributed to the higher blood viscosity. Therefore the authors suggested that the present transfusion triggers could represent in fact viscosity triggers.²⁵

CONCLUSION

Over a wide range of haemoglobin values the organism is capable of maintaining a sufficient O₂ delivery to the tissue provided normovolaemia is maintained. The main compensatory mechanisms are the increase in cardiac output and the increase in oxygen extraction.

Practice points

- Over a wide range of haemoglobin values the organism is capable of maintaining a sufficient O₂ delivery to the tissue provided normovolaemia is maintained.
- The main compensatory mechanisms are the increase in cardiac output and the increase in oxygen extraction.
- The presence of stable coronary artery disease is no contra-indication to acute normovolaemic haemodilution to a haemoglobin of 8–9 g/dl.

Research agenda

- Large scale prospective randomised studies on the impact of restrictive vs. liberal perioperative transfusion triggers.
- Detailed assessment of the impact of patient related co-morbidities on the compensatory mechanisms during acute normovolaemic haemodilution.
- Development of a clinical monitor to assess the adequacy of tissue oxygenation during acute anaemia.

REFERENCES

- *1. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *The New England Journal of Medicine* 1999; **340**: 409–417.

- *2. Vincent JL, Baron JF, Reinhart K et al. Anemia and blood transfusion in critically ill patients. *The Journal of the American Medical Association* 2002; **288**: 1499–1507.
- *3. Corwin HL, Gettinger A, Pearl RG et al. The CRIT Study: anemia and blood transfusion in the critically ill—Current clinical practice in the United States. *Critical Care Medicine* 2004; **32**: 39–52.
4. Hebert PC, Van der Linden P, Biro G et al. Physiologic aspects of anemia. *Critical Care Clinics* 2004; **20**: 187–212.
5. Jamnicki M, Kocian R, van der Linden P et al. Acute normovolemic hemodilution: physiology, limitations, and clinical use. *Journal of Cardiothoracic and Vascular Anesthesia* 2003; **17**: 747–754.
6. Habler OP, Kleen MS, Hutter JW et al. Effects of hyperoxic ventilation on hemodilution-induced changes in anesthetized dogs. *Transfusion* 1998; **38**: 135–144.
7. Habler OP, Kleen MS, Hutter JW et al. Hemodilution and intravenous perflubron emulsion as an alternative to blood transfusion: effects on tissue oxygenation during profound hemodilution in anesthetized dogs. *Transfusion* 1998; **38**: 145–155.
- *8. Pape A, Meier J, Kertscho H et al. Hyperoxic ventilation increases the tolerance of acute normovolemic anemia in anesthetized pigs. *Critical Care Medicine* 2006; **34**: 1475–1482.
9. Kleen M & Messmer K. Toxicity of high PaO₂. *Minerva Anestesiologica* 1999; **65**: 393–396.
- *10. Meier J, Kemming GI, Kisch-Wedel H et al. Hyperoxic ventilation reduces 6-hour mortality at the critical hemoglobin concentration. *Anesthesiology* 2004; **100**: 70–76.
- *11. Suttner S, Piper SN, Kumle B et al. The influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. *Anesthesia and Analgesia* 2004; **99**: 2–11.
- *12. Weiskopf RB, Feiner J, Hopf HW et al. Oxygen reverses deficits of cognitive function and memory and increased heart rate induced by acute severe isovolemic anemia. *Anesthesiology* 2002; **96**: 871–877.
13. Morisaki H & Sibbald WJ. Tissue oxygen delivery and the microcirculation. *Critical Care Clinics* 2004; **20**: 213–223.
14. Habler O, Kleen M, Podtschaske A et al. The effect of acute normovolemic hemodilution (ANH) on myocardial contractility in anesthetized dogs. *Anesthesia and Analgesia* 1996; **83**: 451–458.
15. Spahn DR, Leone BJ, Reves JG et al. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of nonoxygen-carrying and oxygen-carrying solutions. *Anesthesia and Analgesia* 1994; **78**: 1000–1021.
16. Weiskopf RB, Feiner J, Hopf H et al. Heart rate increases linearly in response to acute isovolemic anemia. *Transfusion* 2003; **43**: 235–240.
- *17. Spahn DR, Seifert B, Pasch T et al. Effects of chronic beta-blockade on compensatory mechanisms during acute isovolaemic haemodilution in patients with coronary artery disease. *British Journal of Anaesthesia* 1997; **78**: 381–385.
18. Eagle KA, Berger PB, Calkins H et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002; **105**: 1257–1267.
- *19. Spahn DR, Schmid ER, Seifert B et al. Hemodilution tolerance in patients with coronary artery disease who are receiving chronic beta-adrenergic blocker therapy. *Anesthesia and Analgesia* 1996; **82**: 687–694.
20. Licker M, Ellenberger C, Sierra J et al. Cardiovascular response to acute normovolemic hemodilution in patients with coronary artery diseases: Assessment with transesophageal echocardiography. *Critical Care Medicine* 2005; **33**: 591–597.
21. Licker M, Ellenberger C, Sierra J et al. Cardioprotective effects of acute normovolemic hemodilution in patients undergoing coronary artery bypass surgery. *Chest* 2005; **128**: 838–847.
22. Licker M, Ellenberger C, Murith N et al. Cardiovascular response to acute normovolaemic haemodilution in patients with severe aortic stenosis: assessment with transoesophageal echocardiography. *Anaesthesia* 2004; **59**: 1170–1177.
23. Spahn DR, Seifert B, Pasch T et al. Haemodilution tolerance in patients with mitral regurgitation. *Anaesthesia* 1998; **53**: 20–24.
24. Hebert PC, McDonald BJ & Tinmouth A. Clinical consequences of anemia and red cell transfusion in the critically ill. *Critical Care Clinics* 2004; **20**: 225–235.
- *25. Cabrales P, Martini J, Intaglietta M et al. Blood viscosity maintains microvascular conditions during normovolemic anemia independent of blood oxygen-carrying capacity. *American Journal of Physiology. Heart and Circulatory Physiology* 2006; **291**: H581–H590.



ELSEVIER



2

Physiologic transfusion triggers

Benoit Vallet* MD, PhD

Professor of Anesthesiology and Intensive Care Medicine, Head

Sébastien Adamczyk

Resident

Olivier Barreau

Resident

Gilles Lebuffe MD, PhD

Professor of Anesthesiology and Intensive Care Medicine

Department of Anesthesiology and Intensive Care Medicine, University Hospital of Lille, France

In clinical practice, the decision to transfuse is linked to the hope of increasing oxygen transport (TO_2) to tissues. Physiologic transfusion triggers should progressively replace arbitrary hemoglobin-based transfusion triggers. These 'physiologic' transfusion triggers can be based on signs and symptoms of impaired global oxygenation (lactate, venous O_2 saturation [SvO_2]) or, even better, of regional tissue oxygenation (electrocardiographic ST-segment, electroencephalographic P300 latency). The SvO_2 or its surrogate, the central venous O_2 saturation ($ScvO_2$), is a clinical tool which integrates the relationship between whole-body O_2 uptake and TO_2 , and as such can be proposed as a simple physiologic transfusion trigger.

Key words: oxygen (O_2) transport (TO_2); regional tissue oxygenation; lactate; venous O_2 saturation (SvO_2); central venous O_2 saturation ($ScvO_2$); electroencephalographic P300 latency.

A decrease in hemoglobin (Hb; g/dL) is likely to be associated with a decrease in oxygen transport (TO_2) when cardiac output (CO) remains unchanged, since $TO_2 = CO \times CaO_2$, where CaO_2 is arterial oxygen content, with $CaO_2 \approx Hb \times SaO_2 \times 1.34$ (where

* Corresponding author. Pôle d'Anesthésie & Réanimation, Hôpital Huriez – CHRU de Lille, Rue Michel Polonovski, F59037 – Lille cédex. Tel.: +33 3 20 44 51 96; Fax: +33 3 20 44 44 00.

E-mail address: bvallet@chru-lille.fr (B. Vallet).

SaO₂ is the percentage arterial oxygen saturation; and 1.34 mL oxygen/g Hb is the oxygen-carrying capacity of Hb), if one ignores the negligible O₂ not bound to Hb.¹

In clinical practice, the decision to transfuse is therefore linked to the hope of increasing TO₂ to tissues and subsequent oxygen utilization by the cells.^{2,3} Conversely, one could define sufficient TO₂ as that which meets tissue oxygen needs (VO₂) or as that which favors full cell oxygenation^{4,5}, with $VO_2 = (CaO_2 - CvO_2) \times CO$ according to the Fick equation. Since venous oxygen content is $CvO_2 \approx Hb \times SvO_2 \times 1.34$ (where SvO₂ is the % mixed venous oxygen saturation), VO₂ can be then calculated as: $VO_2 \approx CO \times (SaO_2 - SvO_2) \times Hb \times 1.34$; and SvO₂ can be derived from: $SvO_2 \approx SaO_2 - VO_2 / (Hb \times 1.34 \times CO)$.

VENOUS OXYGEN SATURATION AND THE OXYGEN UPTAKE/DELIVERY RELATIONSHIP

The venous oxygen saturation is a clinical tool which integrates the whole-body VO₂/TO₂ relationship. In the clinical setting, the mixed SvO₂ can be measured (continuously or not) through the distal line of a pulmonary artery catheter (PAC). In the absence of a PAC, the central venous oxygen saturation (ScvO₂) is being increasingly used as a reasonably accurate surrogate.⁶ The normal range for SvO₂ is 68–77% and is considered to be 5% above these values for ScvO₂.⁷

A decrease in Hb is one of the four determinants responsible for a decrease in SvO₂ (or ScvO₂), alone or in combination with hypoxemia (decrease in SaO₂), an increase in VO₂ without a concomitant increase in TO₂, or a fall in CO.

When TO₂ decreases, VO₂ is maintained (at least initially) by an increase in EO₂ (oxygen extraction), since $EO_2 = VO_2 / TO_2$. Since $VO_2 \approx (SaO_2 - SvO_2) \times (Hb \times 1.34 \times CO)$ and $TO_2 \approx SaO_2 \times Hb \times 1.34 \times CO$, $EO_2 \approx (SaO_2 - SvO_2) / SaO_2$. EO₂ and SvO₂ are thus linked by a simple equation: $EO_2 \approx 1 - SvO_2$. Assuming SaO₂ = 1⁸, when SvO₂ is 40%, EO₂ is 60%.

Increased oxygen extraction reflects blood flow alteration at a regional level. This is characterized by redistribution from non-vital to vital organs such as heart and brain, allowing the heart to meet the increased oxygen demand, since myocardial EO₂ reserve is limited and cannot fully compensate for the decreased blood oxygen capacity. In contrast, the cerebral EO₂ can be significantly increased in response to TO₂ decrease. Finally, microcirculatory changes take place, leading to a recruitment of capillaries and homogeneous blood flow through the capillary bed, which in turn enables increased EO₂.⁹

When TO₂ decreases beyond a certain threshold it induces a decrease in VO₂. This point is known as the critical TO₂ (TO₂crit), below which there is a state of oxygen uptake-to-supply dependency which can be defined as shock or dysoxia.^{3,4} Below the TO₂crit, a decrease in consumption (VO₂) is associated with an increase in lactic acid production¹⁰ and an inadequate supply of ATP relative to cellular requirements.¹¹ At this TO₂crit, EO₂ reaches its critical point (EO₂crit). The TO₂crit is highly dependent on VO₂. When VO₂ is higher, TO₂crit is higher as well. TO₂crit is also higher when EO₂crit is lower.

In humans, tissue dysoxia is usually present when SvO₂ falls below 40–50% (SvO₂crit); however, this may also occur at higher levels of SvO₂ when EO₂ is impaired. Usually efforts to correct CO (by fluids or inotropes) and/or Hb and/or SaO₂ and/or VO₂ must target a return of SvO₂ (ScvO₂) from 50 to 65–70%.¹² Hypovolemia due to blood loss is primarily corrected by infusion of crystalloids and colloids

and transformed into normovolemic anemia. Acute normovolemic anemia usually results in an increase in CO.¹³ The decrease in blood viscosity leads to a facilitated venous return with an increased preload, and sympathetic stimulation increases inotropy, thereby contributing further to the increase in CO.

THE CONCEPT OF PHYSIOLOGIC TRANSFUSION TRIGGER

In sedated critically ill patients in whom life support was discontinued, TO_2crit was found to be approximately 3.8–4.5 mL $O_2/kg/min$ for a VO_2 about 2.4 mL $O_2/kg/min$; EO_2 reached an EO_2crit of 60%¹⁴ with SvO_2crit being $\approx 40\%$. In an 84-year-old male Jehovah's Witness undergoing profound hemodilution, the TO_2crit was 4.9 mL $O_2/kg/min$ for a similar VO_2 at about 2.4 mL $O_2/kg/min$; the Hb value at the TO_2crit was 3.9 g/dL.⁵ This Hb value can be defined as a critical Hb value. Consistent with these results, in young, healthy, and conscious (which means higher VO_2 values) volunteers undergoing acute hemodilution with 5% albumin and autologous plasma, TO_2crit was found to be lower than 7.3 mL $O_2/kg/min$ for a VO_2 at 3.4 mL $O_2/kg/min$ ¹⁵ and an Hb value of 4.8 g/dL. The same investigators studied healthy resting humans to test whether acute isovolemic reduction of blood hemoglobin concentration to 5 g/dL would produce an imbalance in myocardial oxygen supply and demand, resulting in myocardial ischaemia.¹⁶ Heart rates increased from 63 ± 11 (baseline measured before hemodilution began) to 94 ± 14 beats/min (a mean increase of $51 \pm 27\%$; $P < 0.0001$), whereas mean arterial blood pressure decreased from 87 ± 10 to 76 ± 11 mmHg (a mean decrease of $12 \pm 13\%$; $P < 0.0001$), mean diastolic blood pressure decreased from 67 ± 10 to 56 ± 10 mmHg (a mean decrease of $15 \pm 16\%$; $P < 0.0001$), and mean systolic blood pressure (SAP) decreased from 131 ± 15 to 121 ± 16 mmHg (a mean decrease of $7 \pm 11\%$; $P = 0.0001$). Electrocardiographic (ECG) changes were monitored continuously using a Holter ECG recorder for detection of myocardial ischemia. During hemodilution, transient, reversible ST-segment depression developed in three asymptomatic subjects at Hb concentrations of 5 g/dL while the subjects were asymptomatic. The subjects who had ECG ST-segment changes had significantly higher maximum heart rates (110–140 beats/min) than those without ECG changes, despite having similar baseline values. The higher heart rates that developed during hemodilution may have contributed to the development of an imbalance between myocardial supply and demand resulting in ECG evidence of myocardial ischemia. An approach of the myocardial oxygen balance is offered by the product $SAP \times HR$ which should remain below 12,000. For $HR = 110$ beats/min, if SAP is 120 mmHg, $SAP \times HR = 13,200$ and may be considered too high for the myocardial VO_2 .

In 20 patients older than 65 years and free from known cardiovascular disease, Hb was decreased from 11.6 ± 0.4 to 8.8 ± 0.3 g/dL. With stable filling pressures, CO increased from 2.02 ± 0.11 to 2.19 ± 0.10 L/min/m² ($P < 0.05$), while systemic vascular resistance decreased from 1796 ± 136 to 1568 ± 126 dynes/s/cm⁵ ($P < 0.05$) and EO_2 increased from 28.0 ± 0.9 to $33.0 \pm 0.8\%$ ($P < 0.05$) resulting in stable VO_2 during hemodilution. While no alterations in ST segments were observed in lead II, ST segment deviation became slightly less negative in lead V_5 during hemodilution from -0.03 ± 0.01 to -0.02 ± 0.01 mV ($P < 0.05$). The authors concluded that isovolemic hemodilution to a hemoglobin value of about 8.8 g/dL was the limit to be tolerated in these patients.¹⁷

In 60 patients scheduled for coronary artery bypass graft surgery with coronary artery disease receiving β -adrenergic blockers chronically, Hb was decreased from

12.6 ± 0.2 to 9.9 ± 0.2 g/dL ($P < 0.05$). With stable filling pressures, CO increased from 2.05 ± 0.05 to 2.27 ± 0.05 L/min/m² ($P < 0.05$) and EO₂ from 27.4 ± 0.6 to $31.2 \pm 0.7\%$ ($P < 0.05$), resulting in stable VO₂. No alterations in ST segments were observed in leads II and V₅ during hemodilution. Individual increases in cardiac index and EO₂ were not linearly related to age and left ventricular ejection fraction ($P = 0.841$; $P = 0.799$).¹⁸

Young healthy volunteers were also tested with verbal memory and standard, computerized neuropsychologic tests before and twice after acute isovolemic reduction of their Hb concentration to 5.7 ± 0.3 g/dL. Heart rate (HR), mean arterial blood pressure (MAP), and self-assessed sense of energy were recorded at the time of each test. Reaction time for digit-symbol substitution test (DSST) increased, delayed memory was degraded, MAP and energy level decreased, and HR increased (all $P < 0.05$). Increasing arterial oxygen pressure (PaO₂) to 406 ± 47 mmHg reversed the DSST result and the delayed memory changes to values not different from those at the baseline Hb concentration of 12.7 ± 1.0 g/dL and decreased heart rate ($P < 0.05$), although MAP and energy level changes were not altered with increased PaO₂ during acute anemia. In that study, the authors confirmed that acute isovolemic anemia subtly slows human reaction time, degrades memory, increases HR, and decreases energy level.¹⁹

Subsequent studies identified the cause of the observed cognitive function deficits in impaired central processing as quantified by measurement of the P300 latency. The P300 response was significantly prolonged when unmedicated healthy volunteers were hemodiluted from hemoglobin concentrations of 12.4 ± 1.3 to 5.1 ± 0.2 g/dL.²⁰ The increased P300 latencies could be reversed to values not significantly different from baseline when inspired oxygen concentration was increased from 21 (room air) to 100%. These results suggest that P300 latency is a variable sensitive enough to predict subtle changes in cognitive function. Accordingly, the increase of the P300 latency above a certain threshold might serve as a monitor of inadequate cerebral oxygenation and as an organ-specific transfusion trigger in the future.

Spahn and Madjdpour²¹ recently emphasized that Weiskopf et al^{20,22} have opened the 'window to the brain' with respect to monitoring the adequacy of cerebral oxygenation during acute anemia.

These observations and results clearly indicate that there is no 'universal' Hb threshold that could serve as reliable transfusion trigger and that transfusion guidelines should take into account the patient's individual ability to tolerate and to compensate for the acute decrease in Hb concentration. Useful transfusion triggers should rather consider signs of inadequate tissue oxygenation that may occur at various hemoglobin concentrations depending on the patient's underlying diseases.¹ These 'physiologic' transfusion triggers can be based on signs and symptoms of impaired global (lactate, SvO₂ or ScvO₂) or, even better, of regional tissue oxygenation (ECG ST-segment, DSST or P300 latency).

THE VENOUS OXYGEN SATURATION AS A PHYSIOLOGIC TRANSFUSION TRIGGER

The venous oxygen saturation helps to assess the VO₂/TO₂ relationship and anemia tolerance during blood loss since it integrates Hb, CO, VO₂ and SaO₂. The mixed SvO₂ can be measured with the help of a PAC. The central venous catheter allows sampling of blood for measurement of ScvO₂, the surrogate for mixed SvO₂, or

even monitoring if an oximetry catheter is being used. A central venous catheter is simpler to insert, and generally safer and cheaper than a PAC.

In a landmark study by Rivers et al²³, patients admitted to an emergency department with severe sepsis and septic shock were randomized to standard therapy (aiming for a CVP of 8–12 mmHg, MAP \geq 65 mmHg, and urine output \geq 0.5 mL/kg/h) or to early goal-directed therapy (EGDT) where, in addition to the previous parameters, an ScvO₂ of at least 70% was targeted by optimizing fluid administration, keeping hematocrit \geq 30%, and/or giving dobutamine to a maximum of 20 μ g/kg/min. The initial ScvO₂ in both groups was low ($49 \pm 12\%$), suggesting a hypodynamic condition before resuscitation is started. From the 1st to the 7th hour the amount of fluid received was significantly larger in the EGDT patients (\approx 5000 mL versus 3500 mL). From the 1st to the 7th hour, and from the 7th to the 72nd hour, the number of patients treated by vasopressor was smaller in EGDT patients (i.e. 27.4 versus 30.3%, and 29.1 versus 42.9% respectively) when the number of patients treated by dobutamine was significantly larger (13.7 versus 0.8% and 14.5 versus 8.4% respectively). When in all patients the decision was to keep a hematocrit above 30%, it is noticeable that the number of patients receiving red blood cells was significantly larger in the EGDT group than in the control group (64.1 versus 18.5%), suggesting that the strategy of targeting a ScvO₂ of at least 70% was associated with more decisions to transfuse once fluid, vasopressor, and dobutamine were titrated to improve tissue oxygenation. In the follow-up period between the 7th and the 72nd hour, in patients receiving EGDT, mean ScvO₂ was higher ($70.6 \pm 10.7\%$ versus $65.3 \pm 11.4\%$; $P=0.02$), mean arterial pH was higher (7.40 ± 0.12 versus 7.36 ± 0.12 ; $P=0.02$), and lactate plasma levels were lower (3.0 ± 4.4 mmol/L versus 3.9 ± 4.4 mmol/L; $P=0.02$), as well as base excess (2.0 ± 6.6 mmol/L versus 5.1 ± 6.7 mmol/L; $P=0.02$). Organ failure score was significantly altered in patients receiving standard therapy when compared to EGDT patients. Hospital mortality fell from 46.5% (standard group) to 30.5% in the EGDT group ($P=0.009$). Importantly, 99.2% of patients receiving EGDT achieved their treatment goals within the first 6 hours compared with 86% in the standard group. This was the first study demonstrating that initiation of EGDT to achieve an adequate level of tissue oxygenation by oxygen delivery (as judged by ScvO₂ monitoring) significantly improves mortality.

In a subsequent prospective observational study²⁴ we tested how well the ScvO₂ was related to the French recommendations for blood transfusion (BT) and to the anesthesiologist's decision to transfuse. The French recommendations for BT were presented during a consensus conference organized in 2003 by the French Society of Intensive Care Medicine (*Société de Réanimation de Langue Française*; SRLF). They are based on plasma Hb concentration value and associated clinical state (Table 1). Apart from cardiac and septic patients, the threshold value of Hb for BT is 7 g/dL. Sixty high-risk surgery patients in whom BT decision was discussed postoperatively were included in the study. They were eligible when hemodynamically stable and equipped with a central venous catheter. The BT decision was taken by the anesthesiologist in charge of the patient. The anesthesiologist was informed of the French recommendations; on request he/she could be aware of the ScvO₂ value that was obtained at the sampling time of the Hb. The following parameters were registered: age, history of cardiovascular disease, presence of sepsis, number of blood units transfused, agreement with the SRLF recommendations. In 53 of the 60 general and urologic surgery patients, the BT was decided. ScvO₂ and Hb were measured before and after BT, together with hemodynamic parameters

Table 1. The French recommendations for blood transfusion (BT) in critically ill patients are based on a recent consensus presented by the French Society of Intensive Care Medicine (*Société de Réanimation de Langue Française*; SRLF) using threshold values for hemoglobin (Hb) together with the clinical context for indicating BT.

Threshold value of Hb (g/dL)	Clinical context
10	Acute coronary syndrome
9	Ischemic heart disease Stable heart failure
8	Age >75 Severe sepsis
7	Others

(HR, SAP). Patients were retrospectively divided into two groups according to ScvO₂ before BT: < or ≥70%, and then in four groups according to the SRLF recommendations (reco) for BT: reco⁺ for 'recommendation for BT'; reco⁻ for 'no recommendation for BT'.

Overall, demographic characteristics were similar (Table 2). BT provided a significant and approximately similar increase in Hb for each patient in the four groups, while ScvO₂ value rose significantly only in reco⁺ patients with ScvO₂ <70% before BT (Table 3). The HR and SAP were of no value in helping the BT decision. We must notice, however, that the SAP × HR product was >12,000 (post-BT HR × SAP = 100 × 130 = 13,000) in the unique situation where reco⁻ patients with an ScvO₂ ≥ 70% were transfused.

The conclusions of this observational study are as follows: (1) 26 patients (49%) received BT in spite of recommendations (reco⁻); (2) 22.6% of the patients out of these recommendations (reco⁻) with an ScvO₂ < 70% seem nevertheless to derive benefit from BT (according to the VO₂/TO₂ relationship); one may speculate that absence of recommendations for BT in those patients could have contributed to a 'lack of BT'; (3) according to ScvO₂ (which remained largely below 70%) BT might even have been insufficient (*n* = 2 blood units) in this subgroup; (4) 24.5% of the patients fulfilling the SRLF recommendations (reco⁺) with an ScvO₂ ≥ 70% received BT, although VO₂/TO₂ might have been adequate; one may speculate that BT in those patients could have contributed to an 'excess of BT', which would be consistent with the post-BT HR × SAP product.

Table 2. Demographic characteristics in 53 patients who received blood transfusion (BT).

Reco	ScvO ₂ < 70% (<i>n</i> = 26)		ScvO ₂ ≥ 70% (<i>n</i> = 27)		Kruskal-Wallis test (<i>P</i> = 0.05)
	- (<i>n</i> = 12)	+ (<i>n</i> = 14)	- (<i>n</i> = 14)	+ (<i>n</i> = 13)	
Age	55.5 [46.4–64.4]	74.5 [62.2–77.2]	46 [30.5–62.9]	69 [59.7–80.3]	NS
Weight	73.5 [62.9–96.9]	74 [67.8–76.8]	70 [58.7–86.7]	70 [57.3–72.5]	NS
Blood units	2 [1.7–2.1]	2 [1.8–2.7]	2 [1.8–2.7]	2 [1.6–2.2]	NS

Patients were divided into two groups according to their central venous oxygen saturation (ScvO₂) before BT: < or ≥70%, and then into four groups according to the SRLF recommendations (reco) for BT: reco⁺ for 'recommendation for BT'; reco⁻ for 'no recommendation for BT'.

Table 3. Central venous oxygen saturation (ScvO₂), hemoglobin (Hb), heart rate (HR) and systolic arterial pressure (SAP) values (median [CI 95%]) in patients divided into two groups as in Table 2.

Reco	ScvO ₂ < 70%		ScvO ₂ ≥ 70%		Kruskal–Wallis test (P < 0.05)
	+	–	+	–	
ScvO ₂ pre-BT	58.6 [52.2–62.3]	56.5 [49.0–62.9]	75.3 [68.0–79.9]	75.4 [58.5–86.9]	P < 0.001
ScvO ₂ post-BT	69.3 ^a [58.8–74.5]	65.4 [55.5–69.7]	77.4 [71.0–80.8]	75.9 [67.7–80.8]	P = 0.002
Hb pre-BT	7.4 [7.2–7.9]	8.0 [7.6–8.5]	7.6 [7.2–8.2]	7.5 [7.3–8.0]	NS
Hb post-BT	9.2 ^a [8.7–9.8]	9.9 ^a [9.4–10.3]	9.7 ^a [9.2–10.6]	10.2 ^a [9.2–10.7]	NS
HR pre-BT	89.0 [84.3–106.1]	95.5 [90.1–112.9]	87.5 [75.8–102.6]	97.0 [86.3–126.6]	NS
HR post-BT	92.0 [86.2–98.9]	92.0 [82.9–101.1]	84.0 [78.7–100.4]	100.0 [84.2–107.5]	NS
SAP pre-BT	120.5 [105.7–138.4]	130.0 [120.7–149.5]	128.0 [117.1–138.7]	124.0 [109.6–150.0]	NS
SAP post-BT	122.0 [111.4–138.3]	120.0 [108.6–146.6]	140.0 ^a [131.8–159.2]	130.0 ^a [117.9–163.5]	NS

^a P < 0.05; Wilcoxon test for values before (pre-BT) versus after BT (post-BT).

Following the study by Rivers et al, and our own observations, we conclude that ScvO₂ appears to be an interesting parameter to help in making a BT decision in hemodynamically unstable severe sepsis or in stable high-risk surgery patients equipped with a central venous catheter. ScvO₂ can be proposed as a simple and universal physiologic transfusion trigger. It deserves a controlled randomized study in which patients would be separated into two treatment groups: (1) a control group in which the BT decision will be made according to Hb threshold values (similar to those presented by the SRLF); (2) an ScvO₂ goal-directed group in which the BT decision will be made according to an ScvO₂ value <70% as soon as the Hb value is <10 g.dL⁻¹ (hematocrit <30%), providing that the CVP is 8–12 mmHg.

Practice points

- ScvO₂ can help in making a blood transfusion (BT) decision in hemodynamically unstable severe sepsis or in stable high-risk surgery patients equipped with a central venous catheter
- the Hb level associated with the knowledge of the clinical context is not predictive of the ScvO₂ value
- the BT decision can be made according to an ScvO₂ value <70% as soon as the Hb value is <10 g/dL (hematocrit <30%) providing that the central venous pressure is 8–12 mmHg

Research agenda

- there is a need for a controlled randomized study in which patients would be separated into two treatment groups: (1) a control group in which the BT decision will be made according to Hb threshold values (similar to those presented by the SRLF); (2) an ScvO₂ goal-directed group in which the BT decision will be made according to an ScvO₂ value <70% as soon as the Hb value falls to <10 g/dL (hematocrit <30%), providing that the CVP is 8–12 mmHg. Main study goals: transfusion savings in the ScvO₂ goal-directed group; adverse events in both groups

CONCLUSION

Physiologic transfusion triggers should progressively replace arbitrary Hb-based transfusion triggers. This will render allogeneic erythrocyte transfusions more efficacious because physicians will be capable of using goal-directed erythrocyte transfusions.²¹ These ‘physiologic’ transfusion triggers can be based on signs and symptoms of impaired global (lactate, SvO₂ or ScvO₂) or, even better, regional tissue oxygenation (ECG ST-segment, DSST or P300 latency). They have to include, however, two important simple hemodynamic targets: HR and MAP or SAP. One may refer to the product SAP × HR which should remain below 12,000 to maintain the myocardial oxygen balance.

REFERENCES

1. Madjdpour C, Spahn DR & Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Critical Care Medicine* 2006; **34**: S102–S108.
- *2. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *Journal of Applied Physiology* 1977; **42**: 228–234.
3. Robin ED. Of men and mitochondria: coping with hypoxic dysoxia. *The American Review of Respiratory Disease* 1980; **122**: 517–531.
- *4. Schumacker PT & Cain SM. The concept of a critical oxygen delivery. *Intensive Care Medicine* 1987; **13**: 223–229.
- *5. van Woerkens EC, Trouwborst A & van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesthesia and Analgesia* 1992; **75**: 818–821.
6. Dueck MH, Klimek M, Appenrodt S et al. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology* 2005; **103**: 249–257.
7. Reinhart K, Kuhn HJ, Hartog C & Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Medicine* 2004; **30**: 1572–1578.
8. Räsänen J. Mixed venous oximetry may detect critical oxygen delivery. *Anesthesia and Analgesia* 1990; **71**: 567–568.
9. Morisaki H & Sibbald WJ. Tissue oxygen delivery and the microcirculation. *Critical Care Clinics* 2004; **20**: 213–223.
10. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *The American Journal of Physiology* 1965; **209**: 604–610.
11. Vallet B, Wiel E & Lebuffe G. Resuscitation from circulatory shock. In Fink MP, Abraham E, Vincent JL & Kochanek PM (eds.). *Textbook of Critical Care*. 5th edn. Philadelphia: Elsevier Saunders ed., 2005, pp. 905–910.

12. Vallet B & Singer M. Hypotension. In Ramsay G (ed.). *Patient-Centred Acute Care Training*. 1st edn. Brussels: European Society of Intensive Care Medicine ed., 2006, pp. 3–9.
- *13. Weiskopf RB, Viele MK, Feiner J et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA: The Journal of the American Medical Association* 1998; **279**: 217–221 [Erratum in: *JAMA* 1998;280:1404].
- *14. Ronco JJ, Fenwick JC, Tweeddale MG et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA: The Journal of the American Medical Association* 1993; **270**: 1724–1730.
- *15. Lieberman JA, Weiskopf RB, Kelley SD et al. Critical oxygen delivery in conscious humans is less than $7.3 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. *Anesthesiology* 2000; **92**: 407–413.
- *16. Leung JM, Weiskopf RB, Feiner J et al. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. *Anesthesiology* 2000; **93**: 1004–1010.
17. Spahn DR, Zollinger A, Schlumpf RB et al. Hemodilution tolerance in elderly patients without known cardiac disease. *Anesthesia and Analgesia* 1996; **82**: 681–686.
18. Spahn DR, Schmid ER, Seifert B & Pasch T. Hemodilution tolerance in patients with coronary artery disease who are receiving chronic beta-adrenergic blocker therapy. *Anesthesia and Analgesia* 1996; **82**: 687–694.
- *19. Weiskopf RB, Feiner J, Hopf HW et al. Oxygen reverses deficits of cognitive function and memory and increased heart rate induced by acute severe isovolemic anemia. *Anesthesiology* 2002; **96**: 871–877.
- *20. Weiskopf RB, Toy P, Hopf HW et al. Acute isovolemic anemia impairs central processing as determined by P300 latency. *Clinical Neurophysiology* 2005; **116**: 1028–1032.
21. Spahn DR & Madjdpour C. Physiologic transfusion triggers: do we have to use (our) brain? *Anesthesiology* 2006; **104**: 905–906.
22. Weiskopf RB, Feiner J, Hopf H et al. Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. *Anesthesiology* 2006; **104**: 911–920.
- *23. Rivers E, Nguyen B, Havstad S, et al, Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *The New England Journal of Medicine* 2001; **345**: 1368–1377.
24. Adamczyk S, Lebuffe G, Robin E et al. ScvO₂: a guide for blood transfusion? *Intensive Care Medicine* 2005; **31**: S123.

TRALI – Definition, mechanisms, incidence and clinical relevance

Pearl Toy* MD

Professor of Laboratory Medicine

University of California San Francisco, San Francisco, CA 94143-0100, USA

Clifford Lowell¹ MD, PhD

Chairman and Professor of Laboratory Medicine

University of California San Francisco, San Francisco, CA 94143-0134, USA

Transfusion-related acute lung injury (TRALI) is defined as new acute lung injury (ALI) that occurs during or within six hours of transfusion, not explained by another ALI risk factor. Transfusion of part of one unit of any blood product can cause TRALI. The mechanism may include factors in unit(s) of blood, such as antibody and biologic response modifiers. In addition, yet to be described factors in a patient's illness may predispose to the condition. The current incidence is estimated to be 1 in 5,000 units. Patients present with acute dyspnea, or froth in the endotracheal tube in intubated patients. Hypertension, hypotension, acute leukopenia have been described. Management is similar to that for ALI and is predominantly supportive. When TRALI is suspected, Blood banks should be notified to quarantine other components from the same donation. No special blood product is required for subsequent transfusion of a patient who has developed TRALI.

Key words: blood transfusion/adverse effects; pulmonary edema; acute lung injury.

Transfusion-related acute lung injury (TRALI) is a syndrome of acute lung injury (ALI) associated with transfusion. The term TRALI was coined by Drs. Popovsky and Moore when they reported a case series at the Mayo Clinic in 1985.¹ In this case series, the typical clinical presentation included acute respiratory distress characterized by hypoxemia and fulminant pulmonary edema. The onset was usually within 4 hours of transfusion and was often accompanied by fever, tachycardia, hypotension or hypertension. In most patients (81%), recovery was rapid and complete. The incidence

* Corresponding author. Tel.: +1 415 353 1671; Fax: +1 415 476 9815.

E-mail addresses: pearl.toy@clinlab.ucsfmedctr.org (P. Toy), clifford.lowell@ucsf.edu (C. Lowell).

¹ Tel.: +1 415 476 2540; Fax: +1 415 502 6497.

was 1:5,000 units transfused and the TRALI patients were comprised of mainly surgical patients. There is still no consensus on the incidence, pathogenesis or laboratory diagnosis of the syndrome. However, reports of TRALI are increasing due to increasing awareness of the syndrome, although underreporting is still strongly suspected. An analysis of the United States Food and Drug Administration fatality reports for the last three fiscal years showed bacterial contamination, TRALI, and ABO hemolytic reactions to be the leading causes of deaths from transfusion. TRALI became the leading cause of fatalities reported to the FDA in fiscal 2003. Fatalities were associated with fresh frozen plasma (FFP), red blood cells (RBCs) or platelets.² Based on these data, it is clear that TRALI is one of the most significant complications of modern blood transfusion. This paper reviews what is known and unknown regarding the definition, mechanisms, incidence and clinical relevance of the syndrome.

DEFINITION

Practice points

- TRALI is a clinical diagnosis
- Suspect TRALI when new ALI develops during or within six hours of transfusion
- Rule out other ALI risk factors such as sepsis and aspiration
- TRALI has been associated with all blood components that contain plasma
- Transfusion of even part of one unit has been associated with TRALI

Definition of ALI

According to the American-European Consensus Conference of acute respiratory distress syndrome³, the criteria for acute lung injury (ALI) are:

- a. Timing: Acute onset
- b. Pulmonary artery wedge pressure: ≤ 18 mm Hg when measured, or a lack of clinical evidence of left atrial hypertension
- c. Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph
- d. Hypoxemia: Ratio of $\text{PaO}_2/\text{FIO}_2 \leq 300$ mm Hg regardless of PEEP level (Note: In patients in whom an arterial blood gas is not available, an oxygen saturation of $< 90\%$ when the patient is breathing room air meets the criterion for hypoxemia)

Definition of clinical TRALI

The National Heart Lung and Blood Institute (NHLBI) Working Group on TRALI developed a definition.⁴ In patients with no ALI immediately before transfusion, and no other ALI risk factor (Table 1) is present, a diagnosis of TRALI is made if there is:

- a. New ALI after transfusion, and
- b. The onset of symptoms or signs is during or within 6 hours after transfusion

Table 1. Risk factors for ALI in prospective studies.^{44,54,55,57}

Risk Factor	Incidence of ALI
Septic shock	47%
Pneumonia source	35%
Extrapulmonary source	13%
Sepsis syndrome without hypotension	29%
Pneumonia source	24%
Extrapulmonary source	6%
Aspiration of gastric contents	15%, 22%, 30%, 36%
Multiple transfusions	36%, 36%, 24%
Near drowning	33%
Disseminated intravascular coagulation	22%
Pulmonary contusion	17%, 22%
Pneumonia requiring ICU care	12%
Drug overdose requiring ICU care	9%
Fracture of long bones or pelvis	5%, 8%, 11%
Burn, any percent of body surface	2%
Cardiopulmonary bypass	2%

The definition includes patients who are massively transfused who develop new ALI, and such patients may be at greater risk for TRALI as they receive multiple units. The definition excludes patients with ALI before transfusion; even though worsening of existing ALI after transfusion could be due to TRALI, defining this form of TRALI is problematic.

In patients who have other ALI risk factors can also develop TRALI, and thus TRALI should not be excluded from consideration in these patients. The incidence of ALI in prospective studies of patient groups with ALI risk factors is less than 50% (see Table 1). Thus, the presence of an ALI risk factor does not mean the patient will definitely develop ALI. New ALI in a transfused patient with an ALI risk factor could be mechanistically due to the transfusion and/or the risk factor, i.e. TRALI and/or ALI due to the risk factor. In such patients who have another ALI risk factor, the diagnosis of TRALI can be difficult. The NHLBI working group recommended that critical care experts judge whether the new ALI is temporally associated with the transfusion, or whether the new ALI is temporally associated with worsening of the other ALI risk factor. The Canadian Consensus Conference proposed no such judgment evaluation and proposed the term “possible TRALI” for new ALI in a transfused patient who also has another ALI risk factor.⁵

Currently there is no definitive laboratory test for the diagnosis of TRALI. Leucopenia or neutropenia has been observed in case reports^{6–12} but has not been studied in small case series.^{1,13} Leukocyte antigen-antibody match between donor and recipient (HLA class I or II, granulocytes or monocytes), and neutrophil priming activity in donor blood have been reported but are not diagnostic.¹⁴

MECHANISMS

Although the association of transfusion with lung injury has been observed for almost 30 years, the mechanisms are still unclear. In massive transfusion, the mechanism of lung injury was initially thought to be microaggregates in stored blood causing

Research agenda

- In patients with other ALI risk factors, research is warranted to determine whether transfusion contributes to new ALI, and whether ALI risk factors predispose patients to TRALI
- Research is warranted to determine whether the mechanism of ALI after multiple transfusions is the same as the mechanism for TRALI after a single unit transfusion.
- Diagnostic laboratory tests for TRALI need to be evaluated in prospective studies

micro-pulmonary emboli and lung damage, but this theory has been discredited, since transfusion of stored blood through microaggregate filters has not prevented lung injury in animals¹⁵ nor in humans.^{16,17} Pathologically, the disease involves sequestration of activated neutrophils within the pulmonary capillaries, leading to acute lung injury.¹⁸ The contribution of neutrophils to multiple types of acute lung injury is well understood and has been validated in several animal models.¹⁹ The major pathophysiologic question in TRALI then becomes how the transfusion is associated with or leads to wide spread neutrophil activation in these patients.

In the past two decades, two hypotheses that lead to neutrophil activation in TRALI have been proposed: antigen-antibody hypothesis versus the two-event hypothesis. Recipient factors that may be involved in the pathogenesis include the recipient's underlying condition and genetic predisposition. Donor unit factors that may be involved in the pathogenesis include leukocyte antibody, cytokines, lipids and factor(s) that increase pulmonary endothelial cell permeability. These hypotheses and factors are discussed below.

The antigen-antibody hypothesis

The first evidence supporting this came from observation that classic findings of TRALI (including leukopenia) developed in a healthy volunteer injected with 50 ml of blood from a patient with a strong leukoagglutinin.⁶ This healthy volunteer was not ill and his neutrophils should not have been primed. In this case, leukocyte antibody alone seemed to cause TRALI. The evidence supporting immunologic activation of neutrophils by antibody revolves around the association of this disease with the presence of anti-HLA class I and II and anti-neutrophil antibodies in the donor units implicated in TRALI. The primary hypothesis is that the alloantibodies in the donor blood product directly activate either the patient neutrophils, monocytes or tissue macrophages, leading to initiation of the inflammatory cascade.^{20,21} Antibodies recognizing neutrophil HNA-2a (CD177) or HNA-3 antigens have been implicated in cellular injury in both *ex vivo* perfused rat lung models and in cell culture models.^{22,23} In both cases, the evidence suggests direct binding of the antibodies to the neutrophils results in cellular activation leading to degranulation and respiratory burst responses, which in turn damage pulmonary endothelium. Donor alloantibodies may also attach directly to vascular endothelial cells, and thus form the equivalent of immune complexes, which in turn recruit circulating neutrophils and lead to sequestration/activation of these cells. This latter hypothesis is supported by the observation of a TRALI reaction occurring in

only one lung following lung transplantation (suggesting that the alloantibodies recognized only new donor lung endothelium).²⁴ This mechanism of alloantibody mediated TRALI has also been modeled in mice, where it was demonstrated that recognition of endothelial bound anti-MHC-I mAb (the murine equivalent of anti-HLA Abs) by neutrophil Fc receptors caused neutrophil activation (degranulation/respiratory burst) and subsequent pulmonary damage.²⁵ Interestingly, it has been observed that the presence of leukocyte antibodies in donors is common, while the occurrence of TRALI is uncommon, and thus antibody alone can not be the sole explanation for TRALI. The incidence of neutrophil antibody of 7.7% in blood donors and components was reported in an abstract.²⁶ The incidence of HLA antibodies has been studied in female donors (not male) and the incidence is dependent on the technique used and donor parity. Using the less sensitive cytotoxicity technique, Rodey found an incidence of 18.7% among donors with a history of four or more pregnancies.²⁷ Densmore found HLA antibodies in 8% of female plateletphereses donors, with frequencies of 7.9% to 26.3% among those with parity between 0 and ≥ 3 pregnancies.²⁸ Insunza found an incidence of 18.1% in female plateletpheresis donors who have had one or more pregnancies.²⁹ Recently, using the sensitive Luminex flow method, investigators at Emory University found HLA antibodies in 22.5% of segments of randomly selected blood components³⁰, but the specificities of these antibodies were not defined.

The two-event hypothesis

Silliman et al noted an association of TRALI cases with use of aged blood products.³¹ They propose that the first event is the patient's condition (surgery, inflammation) that enhances the risk of TRALI. The second event is transfusion of mediators, such as lipids and cytokines from stored blood products, which can prime or directly activate neutrophils, leading to pulmonary damage. These lipids include lysophosphatidylcholines, which are released from apoptotic white blood cells and platelets and have the capacity to enhance neutrophil function.³²

Patient underlying condition

In both hypotheses (either direct antibody mediated activation or the two-event mechanism), it is quite likely that underlying risk factors in patients, including surgery or inflammation, enhance the risk of TRALI reactions. Inflammation has been associated with upregulation of HLA and neutrophil antigens, thus increasing the number of targets for transfused antibody and potentially increasing the probability that transfused antibodies can directly activate neutrophil function.^{33,34} In addition, inflammation may upregulate vascular adhesion molecules such as P, E-selectin and ICAM-I, which in turn will facilitate accumulation of neutrophils in tissues. TRALI may occur if a second hit (ie transfusion of a lipid mediator or cytokine) enhances or directly activates neutrophil function – rapid injury of tissues, such as pulmonary parenchyma, containing the accumulated neutrophils would ensue.

Cytokines

Elevation of cytokines in the plasma of ALI patients, probably as a result of lung injury, has been long observed, and some cytokines are prognostic markers for patient outcome. However, it is also likely that cytokines present in donor blood products can be

directly causative of ALI. Cytokines in the plasma of stored blood products are derived from two sources: leukocytes and platelets, or possibly, from a donor who was incubating an inflammatory but subclinical illness at the time of donation. Proinflammatory cytokines that accumulate with stored red cell blood products are removed by pre-storage leukoreduction, while those that are released by platelet activation may not be removed by leukoreduction. TRALI decreased, but did not disappear, with the implementation of universal leukodepletion in Canada.³⁵ Two reasons account for the decrease in TRALI with leukoreduction: First, the 10% of TRALI cases due to patient antibody against donor leukocytes in the unit of blood would not occur. Second, leukoreduction reduces accumulation of proinflammatory cytokines in stored blood products. During storage of red cells or platelet units that are not leukoreduced, proinflammatory cytokines such as IL-1 β , IL-6, IL-8 and TNF α accumulate in the supernatant plasma, and are virtually eliminated by prestorage leukoreduction.^{36–39} IL-8 has neutrophil priming activity that could be important in causing TRALI.¹⁴ Other cytokines are not reduced by leukoreduction, e.g. RANTES and TGF- β 1 accumulate in platelet components during storage.³⁹ RANTES (Regulated upon activation, normal T-cell expressed and presumably secreted) evokes the release of histamine from basophils, may be related to allergic reactions. There are conflicting data regarding the role of RANTES in animal models of lung injury.^{40,41} TGF- β 1 is mostly bound in an inactive form to extracellular components, but there is evidence of a link to ALI.⁴² PAI-1 is also released by platelets, and but its levels in leukoreduced platelet products is unknown. More recently, direct priming/activation of neutrophils has been demonstrated to occur through the surface molecule CD40, which is recognized by the molecule sCD40L, a major product of platelets and found in high levels in platelet concentrates.⁴³

Genetic predisposition

There is new evidence that there may be genetic predispositions to the development of clinical acute lung injury. For example, polymorphisms in the *SP-B* gene have been associated with the development of ALI.^{44–47} Homozygosity for the deletion polymorphism in the angiotensin converting enzyme (*ACE*) gene which is associated with higher ACE levels and activity was found in an increased frequency among patients with ALI.⁴⁷ Also, there has been some work that associated polymorphisms in the *IL-6* and *TNF- α* genes with susceptibility to sepsis and acute lung injury. Moreover, there has been a growing interest in examining whether common polymorphisms of genes that encode mediators of inflammation, innate immunity, as well as coagulation may allow for host phenotypic differences in the susceptibility to ALI, thus accounting for some of the individual susceptibility to ALI.⁴⁸ Genetic predispositions to TRALI are thus possible but have not yet been defined.

Endothelial cell injury

Another contributor to TRALI reactions is the potential that transfusion products may directly injure vascular endothelial cells in the lung. Recently, Rao et al⁴⁹ have found that supernatants from stored red blood cell units can contain a soluble, transferable factor that directly increases vascular permeability in cultured microvascular endothelial cells. The nature of such an agent, which resulted in partial endothelial cell retraction and development of increased intercellular space, remains unclear. However, the component appears to have a molecular weight greater than 100kD, ruling out

common cytokines. Further investigation of the potential that stored blood products may alter vascular endothelial cell integrity is clearly warranted.

Research agenda

- Research is needed to identify donor or donor unit factors that cause TRALI.
- Research is needed to identify recipient factors that predispose to TRALI

INCIDENCE

The actual incidence of TRALI is unknown because of lack of large, current prospective studies that use a standard definition for the syndrome. The lack of such studies account for the wide range in the reported incidence of TRALI, from approximately 1 in 500 to 1 in 100,000, as reviewed at the consensus conference in Toronto in 2004, including series from University of Denver, University of Alberta, Mayo Clinic, UK, and Canada.⁵⁰ TRALI has been reported following transfusion of all plasma-containing blood components. Estimates of the incidence of TRALI have been 1 in 5,000 components, mostly in whole blood¹, 1 in 7,900 units of fresh frozen plasma⁵¹, and 1 in 432 units of whole blood-derived platelet concentrates.¹³ Critically ill patients may be at greater risk for TRALI because of underlying severe illness, and a retrospective study estimated the risk of TRALI and possible TRALI to be 1 in 1271 units transfused to patients in intensive care units.⁵²

Evidence for underreporting was found in a study of recipients of previous donations of donor with neutrophil 5b antibody. Some patients developed signs and symptoms of TRALI, but these cases had not been reported to the Blood Bank.⁵³ Underreporting is due to several reasons. First, TRALI is acute lung injury (ALI), and there is yet no uniformly agreed upon criteria that distinguish TRALI from ALI³⁴ due to other causes. Second, some clinicians attribute ALI to massive transfusion^{44,54,55}, rather than to TRALI from a single unit of blood. Third, the treatment of TRALI is currently the same as for other forms of ALI, primarily supportive with a lung protective ventilatory strategy, so clinicians who recognize the syndrome may see no reason for reporting the case to the Blood Bank. Fourth, distinguishing between intravascular fluid overload vs. TRALI is difficult. Finally, making a diagnosis of TRALI is costly to Blood Banks. The cost of a complete antibody investigation is several thousand dollars, and in addition, implicated donors may be prohibited from further donations, even if they have donated before without reported adverse reactions in recipients. The cost of investigation and loss of blood donors may understandably bias Blood Bank personnel to attribute pulmonary edema after transfusion to fluid overload rather than TRALI.

These barriers to determination of the actual incidence of TRALI can be overcome. Recognizing the need for a common definition, the NHLBI Working Group on TRALI determined criteria for clinical TRALI.⁴ The common definition described earlier in this paper provides a foundation for studies of incidence. To study true incidence, large prospective studies are needed using a standard protocol. In such studies, a surveillance system is needed that does not depend on clinician reports and will capture all cases of TRALI.⁵⁶ Also, in such studies, experts are needed to assess fluid overload vs. ALI vs.

TRALI and the experts should be blinded to donor unit attributes and donor test results.

Research agenda

- Prospective studies are needed to determine the incidence of TRALI
- Surveillance methods that capture all cases of TRALI are needed

CLINICAL RELEVANCE

Practice points

- Stop the transfusion immediately if TRALI is suspected.
- Obtain a white blood cell count and chest radiograph.
- Request Blood Bank to quarantine other units from the same donation(s).
- Request other units for transfusion if indicated (no special requirements).
- Follow institutional policies for a transfusion reaction workup.
- Return bags of units of blood transfused in the last 6 hours, indicating the last unit transfused prior to onset of signs or symptoms

Patients with TRALI present with acute dyspnea during or within hours of transfusion. Intubated patients develop oxygen desaturation and froth may be observed in the endotracheal tube if the patient is supine. For acute management, any transfusion should be stopped immediately and supportive care provided to the patient. A white blood cell count should be obtained soon, as acute leucopenia may develop immediately after transfusion of an implicated unit.¹² The leucopenia may be easily missed later, because the white blood cell count returns to normal within hours, when the marginating pool of neutrophils move into the circulation. The Blood Bank should be notified to quarantine other units from the same donation(s). If the patient requires further transfusions, no special blood products are required. The institutional policies for a transfusion reaction workup should be followed. If available, bags of units of blood transfused in the six hours before onset of signs and symptoms should be returned to the Blood Bank. To facilitate workup, it is helpful to indicate the order the units of blood were transfused, and which unit was transfused during or just prior to onset of signs and symptoms. To determine whether leukocyte antibody was transfused to recipient cognate antigens, blood banks may test for leukocyte antigens in the recipient and leukocyte antibodies in implicated donors units. With supportive therapy, most patients recover without permanent pulmonary disease.

The best strategy to prevent TRALI is unknown because the etiology and pathogenesis of the condition is unclear. However, plasma is currently being diverted from FFP manufacture when the donor is female, on the hypothesis that females are more likely to contain alloreactive antibodies that may induce TRALI in recipient patients. Aside from diversion of all female plasma, other possible strategies include:

- Preventative HLA and granulocyte antibody testing, and/or questioning of female donors on parity, followed by plasma product diversion and washing of red blood cells from donors at increased risk.
- Plasma product diversion of donors involved in a case of TRALI

Research agenda

- Modeling the impact of donor deferral or screening interventions, and
- Research into etiology, diagnostic testing, epidemiology, treatment, and prevention.

SUMMARY

TRALI is clinically defined as new ALI that develops during or within hours of transfusion of any blood product. In the absence of another ALI risk factor such as sepsis, pneumonia or aspiration, and when onset clearly develops after the transfusion, the diagnosis is clear. However in the presence of another ALI risk factor, the new ALI may be caused by the transfusion and/or the ALI risk factor. The mechanism of TRALI is unclear and may be multifactorial, including donor and recipient factors. The incidence was 1:5,000 units transfused in older studies, and new studies need to be performed to determine current incidence among transfusion recipients, especially those in intensive care units. The condition is under diagnosed and anesthesiologists should be aware of the possibility in their patients who develop new ALI after transfusion. Treatment is supportive. Research is much needed to elucidate the mechanisms and to institute effective methods to prevent the disease.

ACKNOWLEDGEMENTS

This work was supported by a Public Health Service grant P50 HL081027 from the National Heart Lung and Blood Institute, National Institutes of Health, USA.

REFERENCES

- *1. Popovsky MA & Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985; **25**: 573–577.
2. Holness L, Knippen MA, Simmons L & Lachenbruch PA. Fatalities caused by TRALI. *Transfusion Medicine Reviews* 2004; **18**: 184–188.
- *3. Bernard GR, Artigas A, Brigham KL et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *American Journal of Respiratory and Critical Care Medicine* 1994; **149**(3 Pt 1): 818–824.
- *4. Toy P, Popovsky MA, Abraham E et al. Transfusion-related acute lung injury: Definition and review. *Critical Care Medicine* 2005; **33**: 721–726.
- *5. Kleinman S, Caulfield T, Chan P et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004; **44**: 1774–1789.
6. Brittingham TE. Immunologic studies on leukocytes. *Vox Sanguinis* 1957; **2**: 242–248.
7. Yomtovian R, Kline W, Press C et al. Severe pulmonary hypersensitivity associated with passive transfusion of a neutrophil-specific antibody. *Lancet* 1984; **1**: 244–246.

8. Cooling L. Transfusion-related acute lung injury. *JAMA: The Journal of the American Medical Association* 2002; **288**: 315–316.
9. Ausley Jr. MB. Fatal transfusion reactions caused by donor antibodies to recipient leukocytes. *The American Journal of Forensic Medicine and Pathology* 1987; **8**: 287–290.
10. Leger R, Palm S, Wulf H et al. Transfusion-related lung injury with leukopenic reaction caused by fresh frozen plasma containing anti-NBI. *Anesthesiology* 1999; **91**: 1529–1532.
11. Wallis JP, Haynes S, Stark G et al. Transfusion-related alloimmune neutropenia: an undescribed complication of blood transfusion. *Lancet* 2002; **360**: 1073–1074.
- *12. Nakagawa M & Toy P. Acute and transient decrease in neutrophil count in transfusion-related acute lung injury: cases at one hospital. *Transfusion* 2004; **44**: 1689–1694.
- *13. Silliman CC, Boshkov LK, Mehdizadehkashi Z et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003; **101**: 454–462.
- *14. Silliman CC, Dickey WO, Paterson AJ et al. Analysis of the priming activity of lipids generated during routine storage of platelet concentrates. *Transfusion* 1996; **36**: 133–139.
15. Geelhoed GW & Bennett SH. “Shock lung” resulting from perfusion of canine lungs with stored bank blood. *The American Surgeon* 1975; **41**: 661–682.
16. Snyder EL, Underwood PS, Spivack M et al. An in vivo evaluation of microaggregate blood filtration during total hip replacement. *Annals of Surgery* 1979; **190**: 75–79.
17. Snyder EL, Hezzy A, Barash PG & Palermo G. Microaggregate blood filtration in patients with compromised pulmonary function. *Transfusion* 1982; **22**: 21–25.
18. Dry SM, Bechard KM, Milford EL et al. The pathology of transfusion-related acute lung injury. *American Journal of Clinical Pathology* 1999; **112**: 216–221.
19. Abraham E. Neutrophils and acute lung injury. *Critical Care Medicine* 2003; **31** (4 supplement): S195–S199.
20. Kopko PM, Popovsky MA, MacKenzie MR et al. HLA class II antibodies in transfusion-related acute lung injury. *Transfusion* 2001; **41**: 1244–1248.
21. Kopko PM, Paglieroni TG, Popovsky MA et al. TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. *Transfusion* 2003; **43**: 177–184.
- *22. Sachs UJ, Hattar K, Weissmann N et al. Antibody-induced neutrophil activation as a trigger for transfusion-related acute lung injury in an ex vivo rat lung model. *Blood* 2006; **107**: 1217–1219.
- *23. Silliman CC, Curtis BR, Kopko PM et al. Donor antibodies to HNA-3a implicated in TRALI reactions prime neutrophils and cause PMN-mediated damage to human pulmonary microvascular endothelial cells in a two-event, in vitro model. *Blood* 2007; **109**: 1752–1755.
24. Dykes A, Smallwood D, Kotsimbos T & Street A. Transfusion-related acute lung injury (Trali) in a patient with a single lung transplant. *British Journal of Haematology* 2000; **109**: 674–676.
- *25. Looney MR, Su X, Van Ziffle JA et al. Neutrophils and their Fc gamma receptors are essential in a mouse model of transfusion-related acute lung injury. *The Journal of Clinical Investigation* 2006; **116**: 1615–1623.
26. Lubenko A & Brough S. The incidence of granulocyte antibodies in female blood donors: Results of screening by a flow cytometric technique. *Platelets* 1994; **5**: 234–235.
27. Rodey GE, Kunicki J, Anderson J & Aster RH. Procurement and identification of HL-A lymphocytotoxic antibodies in sera of nonpregnant, multiparous blood donors. *Transfusion* 1974; **14**: 167–170.
28. Densmore TL, Goodnough LT, Ali S et al. Prevalence of HLA sensitization in female apheresis donors. *Transfusion* 1999; **39**: 103–106.
29. Insunza A, Romon I, Gonzalez-Ponte ML et al. Implementation of a strategy to prevent TRALI in a regional blood centre. *Transfusion Medicine (Oxford, England)* 2004; **14**: 157–164.
30. Bray RA, Harris SB, Josephson CD et al. Unappreciated risk factors for transplant patients: HLA antibodies in blood components. *Human Immunology* 2004; **65**: 240–244.
31. Silliman CC, Paterson AJ, Dickey WO et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. *Transfusion* 1997; **37**: 719–726.
32. Silliman CC, Elzi DJ, Ambruso DR et al. Lysophosphatidylcholines prime the NADPH oxidase and stimulate multiple neutrophil functions through changes in cytosolic calcium. *Journal of Leukocyte Biology* 2003; **73**: 511–524.
33. Girdlestone J. Regulation of HLA class I loci by interferons. *Immunobiology* 1995; **193**: 229–237.
34. Stroncek D. Neutrophil alloantigens. *Transfusion Medicine Reviews* 2002; **16**: 67–75.
35. Yazer MH, Podlosky L, Clarke G & Nahirniak SM. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. *Transfusion* 2004; **44**: 10–15.

36. Weisbach V, Wanke C, Zingsem J et al. Cytokine generation in whole blood, leukocyte-depleted and temporarily warmed red blood cell concentrates. *Vox Sanguinis* 1999; **76**: 100–106.
37. Jacobi KE, Wanke C, Jacobi A et al. Determination of eicosanoid and cytokine production in salvaged blood, stored red blood cell concentrates, and whole blood. *Journal of Clinical Anesthesia* 2000; **12**: 94–99.
38. Seghatchian J & Krailadsiri P. Current position on preparation and quality of leucodepleted platelet concentrates for clinical use. *Transfusion Science* 2000; **22**: 85–88.
39. Fujihara M, Ikebuchi K, Wakamoto S & Sekiguchi S. Effects of filtration and gamma radiation on the accumulation of RANTES and transforming growth factor-beta1 in apheresis platelet concentrates during storage. *Transfusion* 1999; **39**: 498–505.
40. Gerard C, Frossard JL, Bhatia M et al. Targeted disruption of the beta-chemokine receptor CCR1 protects against pancreatitis-associated lung injury. *The Journal of Clinical Investigation* 1997; **100**: 2022–2027.
41. Bless NM, Huber-Lang M, Guo RF et al. Role of CC chemokines (macrophage inflammatory protein-1 beta, monocyte chemoattractant protein-1, RANTES) in acute lung injury in rats. *Journal of Immunology* 2000; **164**: 2650–2659.
42. Pittet JF, Griffiths MJ, Geiser T et al. TGF-beta is a critical mediator of acute lung injury. *The Journal of Clinical Investigation* 2001; **107**: 1537–1544.
43. Khan SY, Kelher MR, Heal JM et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. *Blood* 2006; **108**: 2455–2462.
44. Gong MN, Wei Z, Xu LL et al. Polymorphism in the Surfactant Protein-B Gene, Gender, and the Risk of Direct Pulmonary Injury and ARDS. *Chest* 2004; **125**: 203–211.
45. Max M, Pison U & Floros J. Frequency of Ap-B and SP-A1 gene polymorphism in the acute respiratory distress syndrome (ALI). *Applied Cardiopulmonary Pathophysiology* 1996; **6**: 111–117.
46. Lin Z, Pearson C, Chinchilli V et al. Polymorphisms of human SP-A, SP-B, and SP-D genes: association of SP-B Thr131Ile with ARDS. *Clinical Genetics* 2000; **58**: 181–191.
47. Marshall RP, Webb S, Hill MR et al. Genetic polymorphisms associated with susceptibility and outcome in ARDS. *Chest* 2002; **121**(3 supplement): 68S–69S.
48. Matthay MA. *Acute Respiratory Distress Syndrome*. New York, NY: Dekker, 2003.
49. Rao RS, Howard CA & Teague TK. Pulmonary endothelial permeability is increased by fluid from packed red blood cell units but not by fluid from clinically-available washed units. *The Journal of Trauma* 2006; **60**: 851–858.
50. Goldman M, Webert KE, Arnold DM et al. Proceedings of a Consensus Conference: Towards an Understanding of TRALI. *Transfusion Medicine Reviews* 2005; **19**: 2–31.
51. Wallis JP, Lubenko A, Wells AW & Chapman CE. Single hospital experience of TRALI. *Transfusion* 2003; **43**: 1053–1059.
52. Rana R, Fernandez-Perez ER, Khan SA et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. *Transfusion* 2006; **46**: 1478–1483.
53. Kopko PM, Marshall CS, MacKenzie MR et al. Transfusion-related acute lung injury: report of a clinical look-back investigation. *JAMA: The Journal of the American Medical Association* 2002; **287**: 1968–1971.
54. Pepe PE, Potkin RT, Reus DH et al. Clinical predictors of the adult respiratory distress syndrome. *American Journal of Surgery* 1982; **144**: 124–130.
55. Hudson LD, Milberg JA, Anardi D & Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**(2 Pt 1): 293–301.
56. Finlay HE, Cassorla L, Feiner J & Toy P. Designing and testing a computer-based screening system for transfusion-related acute lung injury. *American Journal of Clinical Pathology* 2005; **124**: 1–9.
57. Fowler AA, Hamman RF, Good JT et al. Adult respiratory distress syndrome: risk with common predispositions. *Annals of Internal Medicine* 1983; **98**(5 Pt 1): 593–597.

The impact of storage on red cell function in blood transfusion

Emre Almac MD

Research Fellow

Can Ince* PhD

Professor of Clinical Physiology

Clinical Physiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Despite the common use of red-blood-cell transfusions in clinical practice, actual beneficial effects of red blood cells have never been demonstrated. On the contrary, several studies suggest that red-blood-cell transfusions are associated with higher risks of morbidity and mortality. The effects of the duration of storage on the efficacy of red blood cells have therefore been questioned in a number of studies. Recent insights into the physiology of red blood cells – such as the role of the hypoxia-induced vasodilator-releasing function of red blood cells – is discussed in relation to the controversy surrounding the use of blood transfusions in clinical practice.

Key words: red blood cell; tissue oxygenation; microcirculation; blood transfusion; transfusion triggers; storage.

HISTORICAL BACKGROUND

The unique function of blood was known by many early civilizations long before the scientific era. It was believed to have a healing ability and to be associated with life, figuring in various beliefs and myths.

The first known transfusion attempt was made, according to legend, in the 15th century, when the blood of three healthy boys was transfused into the veins of the then sick pope Innocentius VIII, unfortunately without success. Two centuries later a Frenchman, Jean-Baptiste Denis, transfused the blood of a calf into a man.

* Corresponding author:

E-mail address: c.ince@amc.uva.nl (C. Ince).

However, up to the beginning of the 20th century more than a half of the transfused patients died, threatening the development of transfusion medicine. This changed as a result of the findings of Karl Landsteiner who, while investigating failed blood transfusions, identified different blood types, resulting in the ABO and rhesus blood group systems. The development of cross-matching strongly decreased adverse transfusion reactions. A second important development in blood transfusion practice was the introduction by Richard Lewisohn in 1915 of sodium citrate as an anticoagulant storage solution. This important development turned the transfusion of blood into a relatively safe and bearable procedure for both the donor and the patient.

The rapidly evolving transfusion technology solved the problem of short storage time, which became an issue during the Second World War due to the need for large amounts of blood. The development of plastic containers eased the storage and transport of blood units. In the 1950s the separation of blood components, and in the last three decades the developments of additive solutions, rejuvenation and leukodepletion fuelled by the increasing demand for allogeneic red-blood-cell transfusions, significantly improved the quality of stored red blood cells.

RED-BLOOD-CELL PHYSIOLOGY AND ITS ROLE IN OXYGEN DELIVERY TO THE TISSUES

In order to understand the impact of storage on the function of red blood cells it is necessary to review normal red-blood-cell physiology and its role in oxygen delivery to the tissues.

Oxygen delivery to the tissues, in general, is simply calculated as the product of blood flow and arterial oxygen content. This can be described as follows:

$$DO_2 = Q(\text{flow}) \times CaO_2(\text{arterial oxygen content})$$

$$CaO_2 = (\text{Hb} \times SaO_2 \times 1.34) + (\text{PaO}_2 \times 0.003)$$

in which 1.34 represents the oxygen-binding capacity of haemoglobin (mL O₂/g Hb) and 0.003 the solubility coefficient for oxygen in blood (0.003 mL O₂ is dissolved for each mmHg of partial O₂ pressure).

It is obvious from this formula that the decreases in flow, arterial oxygen content (a decrease in red-blood-cell mass or haemoglobin oxygen saturation, or an inability to use the oxygen available in the circulation), and dissolved oxygen should result in tissue hypoxia. It is also obvious that decreases in the variables can be compensated, up to a point, by regulation of other variables.

Pathological conditions such as a decrease in haemoglobin levels during anaemia is tolerated to a certain extent by the action of compensatory mechanisms such as increased blood flow. In addition, a moderate decrease in haematocrit can improve oxygen transport by lowering blood viscosity, thereby improving microvascular perfusion. With this in mind, an optimal haematocrit can be predicted which is lower than the physiological haematocrit. On the other hand, lowering blood viscosity too much, as can happen in haemodilution, can cause a fallout of capillaries and a reduction in functional capillary density.^{1,2}

In healthy adults, tissue oxygenation has a residual capacity. In general, oxygen consumption is approximately one third of oxygen delivery, which allows the body to continue its functions in various conditions, where the changes in DO₂ do not affect VO₂ and tissues do not often encounter hypoxia. Thanks to this residual capacity, a wide range of decreases, causing a decrease in oxygen transport capacity, can be compensated for simply by increases in cardiac output. This was shown by van der

Linden and co-workers, who found that fresh red blood cells were as efficient as blood-flow increases in relieving conditions dependent on oxygen supply.

If the decrease in oxygen-carrying capacity is more than the compensatory mechanisms can handle, further decreases in oxygen delivery (DO_2) can lead to an increase in extraction ratio ($ER = VO_2/DO_2$). Upon reaching a critical point, further reduction in haemoglobin concentration causes oxygen supply to be dependent on VO_2 . Further decreases in DO_2 will result in decreases in VO_2 and leave the tissues hypoxic, and if not corrected this may lead to irreversible tissue damage and organ failure. If such a condition is imminent and decreases in systemic haemoglobin levels occur, the therapy of choice is the administration of blood transfusions.

However, as seen from the viscosity example above, oxygen flux into the tissues and finally into the cells also depends on many other factors, such as blood-flow distribution between organs and within the microcirculation, functional capillary density, red-blood-cell transit times, physical, rheological and functional properties of red blood cells, tissue diffusion coefficient, oxygen transport across the cell membrane, and finally mitochondrial function and oxygen requirement.

The microcirculation has an oxygen-dependent regulatory system which is connected to the systemic circulation, but is also able to regulate and direct blood flow to the tissues depending on the metabolic need of those tissues. The flow of blood in the microcirculation, even under normal conditions, is highly heterogeneous, but by its heterogeneity ensures a homogenous distribution of oxygen in the tissues.³ Therefore, in order to regulate microcirculatory blood flow and thereby oxygen transport to the microcirculation instantly, hypoxia-detecting mechanisms are required. Under normal physiological conditions, this finely regulated system of capillaries, arterioles and venules can supply oxygen in excess of oxygen demand, so that the tissues can continue their function under changing metabolic demands.

THE PHYSIOLOGY OF RED BLOOD CELLS

Besides the negligible amount of oxygen dissolved in plasma, red blood cells are the only cell group responsible for the transport of oxygen to and carbon dioxide from the tissues. In order to fulfil this role, red blood cells use haemoglobin molecules which they produce during their maturation process. The unique ability of haemoglobin to bind tightly to oxygen in the lungs and to release it in the tissues where it is needed stems from the allosteric function of 2,3-diphosphoglycerate (2,3-DPG) produced by the Rapoport–Luebering shunt of the Embden–Myerhof pathway. The significance of 2,3-DPG lies in its ability to lower the affinity of the haemoglobin molecule for oxygen, reflected in a right shift of the haemoglobin–oxygen dissociation curve. This function depends on the amount of oxygen bound to the molecule, the pH of the molecule's environment, and the amount of 2,3-DPG present.

When haemoglobin is fully deoxygenated, the molecule exists in the 'taut' configuration (T state). In this conformation, each of the four haem iron atoms has a low binding affinity for oxygen. When an oxygen atom binds to any one of the four iron atoms in the haem rings, the 2,3-DPG molecule cannot access its binding site, conferring a high oxygen-binding affinity on the remaining haem iron atoms (relaxed or R state).

Red blood cells anaerobically catabolize glucose to lactic acid via the Embden–Myerhof or glycolytic pathway. Since red blood cells do not store glycogen, they must constantly catabolize glucose from the bloodstream via this pathway and the hexose monophosphate shunt in order to obtain energy.

The Embden–Myerhof pathway serves three functions in the red blood cell. The first function is ATP production. Production of ATP is essential for a functioning red blood cell. ATP is the major fuel source of red blood cells, and while several enzymes depend on ATP, the $\text{Na}^+\text{-K}^+$ pump in particular is vital for these cells. The red blood cell's volume is maintained largely by the $\text{Na}^+\text{-K}^+\text{-ATPase}$ in its plasma membrane, which extrudes Na^+ from the cell together with osmotically obligated water molecules. In the absence of ATP, Na^+ is retained and the cell swells. Resultant swollen red blood cells fail to negotiate the microcirculation and are eliminated by macrophages. The second function is the production of 2,3-DPG by an alternative pathway called the Rapoport–Luebering shunt. The third function is NADH production, which is essential for additional critical protection against oxidative damage to the cell from toxic peroxide radicals.

In addition to their oxygen-transporting ability with haemoglobin and the allosteric regulator 2,3-DPG, red blood cells need to be able to travel through a fine network of vessels with diameters $<100\ \mu\text{m}$ where the gas exchange actually takes place: the so-called microcirculation. Normally, erythrocytes have a flexible membrane and can reversibly alter their biconcave, discoid shape, which allows them to pass through capillaries smaller in diameter ($2\text{--}6\ \mu\text{m}$) than red blood cells ($\pm 8\ \mu\text{m}$). To maintain the asymmetric membrane structure, biconcave shape, deformability, surface–volume relationship, intracellular viscosity and other physical properties which allow this flexible structure, red blood cells need energy and hence an adenine nucleotide pool in order to synthesize ATP. The compliant nature of red blood cell membranes (in contrast to the stiffer membranes of leucocytes) is of great importance in this respect, ensuring the successful entrance of the cells into the capillaries (the exchange site), thereby allowing adequate oxygen delivery to the tissues. This property of red blood cells also acts as an in-vivo quality control marker, where stiff old cells are filtered in the spleen and cleared by phagocytes from the circulation.

Besides being a cell without a nucleus and being responsible for oxygen and carbon dioxide transport between organs and lungs, new functions of red blood cells have been found which have led to the idea that red blood cells also play an important role in vascular regulation. Increasing numbers of studies have demonstrated that red blood cells induce vasodilation in the presence of hypoxia and promote oxygen transport. Two major compounds have been proposed in relation to this function: ATP and nitric oxide (NO).^{3–8}

ATP

It has become increasingly clear that, in addition to functioning as an intracellular energy source, ATP can serve as important extracellular signalling molecule. It is now known that red blood cells release ATP in response to hypoxia, pH and mechanical stress.

In mechanical stress, the defects of the spectrin network induced by the deformation of red blood cell⁹ were proposed to play a role in the release of ATP from deformed red blood cells. It is suggested that the partially freed actin at these defect sites may explain the activation of the cystic fibrosis transmembrane protein receptor (CFTR) membrane-bound protein and the subsequent release of ATP by red blood cells subjected to deformations.

In hypoxia, however, Jagger et al¹⁰ suggested that the conformational transitioning of oxygenated haemoglobin (R state) to deoxygenated haemoglobin (T state) due to

oxygen release caused by the decreasing gradient of pO_2 leads to the displacement of phosphofructokinase (PFK) from the cytoplasmic domain of band 3 protein, creating increased glycolysis and ATP accumulation within the red blood cell. Subsequently ATP efflux from the red blood cell is believed to occur via CFTR, allowing ATP to activate endothelial purinergic receptor subtypes, increasing the production of nitric oxide. Extracellular ADP as a product of released ATP, and nitric oxide released from the endothelial cells, are proposed to inhibit further ATP release from the red blood cells. Such a feedback mechanism should protect the organism, since the adenosine concentration inside the red blood cells is almost a 1000-fold higher than that in plasma, and 40% of blood consists of red blood cells.

Nitric oxide

It has been proposed that nitric oxide release during hypoxia is associated with the bioavailability of S-nitrosothiol¹¹ and/or nitrate¹² and nitrite⁷ in red blood cells, both of which are able to donate nitric oxide under hypoxic condition. The first studies regarding nitric oxide focused on the endothelial synthesis of nitric oxide products as a result of ATP release from the red blood cells. However, the recent discovery of a functional endothelial nitric oxide synthase (eNOS) in the red-blood-cell membrane that co-localizes with glycophorin A may also be an important component in this respect.⁸ Such hypoxia-induced, red-blood-cell-associated release of vasodilator substances is now regarded as an important vascular regulatory mechanism, ensuring an oxygen supply adequate for the needs of tissues. However important these vascular control mechanisms may be, other red-blood-cell functions are also important determinants of the ability of red blood cells to deliver oxygen to the tissues.

THE IMPACT OF BLOOD STORAGE

Continued developments in storage techniques have resulted in improved storage times as well as red-blood-cell quality. In this context we refer to 'storage' as liquid preservation, as this is the most common blood preservation technique currently in use. The increasing demand for allogeneic blood transfusions has resulted in millions of liquid-stored allogeneic red blood cell units being used annually for transfusions worldwide. This practice is based on the theoretical expectation that increasing the intravascular mass of red blood cells will increase oxygen delivery to the tissues. However, accumulating evidence is showing that this expectation may not be true, and that there is a negative relationship between the storage time and red-blood-cell viability and function. Additionally, recent findings in observational studies on large populations showed that restrictive transfusion triggers were associated with a better patient outcome. Nevertheless, despite these new findings, and the possibility of using allogeneic blood transfusion alternatives – such as peri/postoperative cell salvage, pre-donation and recombinant erythropoietin administration – liquid-stored allogeneic red blood cells are still the most favoured transfused blood products.

The increasing concerns about the efficacy of allogeneic blood transfusions forces the question about the impact of storage on red-blood-cell function and hence on their use for blood transfusion. First, however, the issue of how the physical and biochemical properties of red blood cells are altered under conditions of storage should be discussed. Indeed, it has been shown that red blood cells undergo a number of changes during liquid storage which affect their viability and their ability to deliver

oxygen to the tissues. We can classify the alterations in two major groups: biomechanical and biochemical.

Biomechanical changes

The first group of changes in red-blood-cell properties is membrane alteration. The structure of the red blood cell is complex, and membrane phospholipids and proteins, cytoskeletal proteins and cytoplasmic components are all related to each other.

Haemorheological alterations – such as red blood cell shape changes, decreased membrane deformability and surface/volume ratio, increased mean cell haemoglobin concentration and osmotic fragility, increased aggregability and intracellular viscosity – can occur during storage and may possibly disturb the flow of red blood cells through the microcirculation and influence red-blood-cell transport of oxygen to the tissues.

During storage, red cells undergo progressive morphological changes, from deformable biconcave disks to echinocytes with protrusions, and finally to spherocytocytes. In parallel with these changes, redistribution and loss of phospholipids in the red-cell membrane by the formation of microvesicles are seen both in storage and in red cell aging, and may contribute to these changes during storage.^{13–16}

The storage-related decrease in red-blood-cell membrane deformability is a crucial change in red-blood-cell properties and is associated with post-transfusional 24-hour survival. The decreased deformability was thought to be associated with reduced ATP levels. While ATP depletion as seen during storage can reproduce many shape changes, a reduction in surface/volume ratio and increases in intracellular viscosity and post-transfusional 24-hour survival of red blood cells precede the decreases in ATP concentration. Only decreases beyond 50% of the ATP concentration can be shown to be associated with decreased mortality, suggesting that the role of ATP depletion in storage-related damage may be limited. Nevertheless, restoring ATP levels in red-blood-cell units appears to correct membrane alterations to a certain level. It is probable that a basal ATP level is necessary for the survival of red cells, and therefore the adenine pool (AMP, ADP, and ATP) has more effect on cellular changes than ATP alone.

Other mechanisms – such as loss or redistribution of membrane phospholipids and protein and lipid oxidations – have been suggested to contribute to the storage-dependent alterations of red-blood-cell membranes. The formation of microvesicles, causing the loss of membrane phospholipids, was identified by Rumsby et al.¹⁶ An alternative mechanism which has been proposed is the internalization of phosphatidylserine (PS) and phosphoethanolamine (PE) from the membrane into the cytosol and loss of asymmetry in the red cell membrane.¹⁷ This suggestion is supported by a recent study by Verhoeven et al.¹⁸ in which the effects of prolonged storage on two different activities affecting the red-blood-cell membrane asymmetry were compared. They studied the effects of storage on flippase, the ATP-dependent aminophospholipid translocase, which moves PS from the outer to the inner leaflet of membrane, compared to phospholipid scrambling which moves PS from the inner to outer leaflet. They demonstrated a decrease in flippase activity starting after 21 days of storage in SAGM (saline, adenine, glucose, mannitol) solution and further decreasing over time. The authors also showed that the correction of storage-induced metabolic changes by increasing intracellular ATP levels only partially restores flippase activity. However, flippase activity could be completely restored when intracellular pH was corrected in parallel with ATP.

In conclusion, the red-blood-cell membrane is certainly adversely affected by storage; however, these alterations appear to be reversible, up to a point, by the use of better storage and rejuvenation solutions. Around one fifth to one fourth of transfused red blood cells are being destroyed within the 24 hours of transfusion. This phenomenon may be explained by changes in red-blood-cell membrane structure triggering immune removal mechanisms, so that these old cells are cleared from the circulation. Band 3 protein, a major membrane protein of the erythrocyte in addition to its suggested involvement in oxygen delivery, is also responsible for triggering the binding of antibodies to antigens and the clearance of these cells from the circulation. Very possibly this mechanism is involved in determining the survival of erythrocytes after transfusion. Other proteins, such as annexin V and CD47, are also proposed to contribute to determination of survival or clearance of red blood cells *in vivo*. While annexin V is a cytosolic protein and is investigated as a sensitive marker for monitoring the potential cellular damage induced by filtration of stored whole blood, CD47 is a cell adhesion molecule, and red blood cells lacking CD47 are believed to be rapidly cleared from circulation by the reticuloendothelial system.^{19–21}

These biomechanical alterations may account for less deformable red blood cells, and may cause even more problems for a microcirculation already under stress under conditions of disease. However, biomechanical alterations are probably not the only problem occurring during storage.

Biochemical changes

2,3-DPG

2,3-DPG is a well-known molecule in red-blood-cell function, as its role in haemoglobin oxygen affinity regulation is crucial for tissues. Therefore, any alteration of 2,3-DPG is believed to be very important, and initial studies on the loss of oxygen-delivering ability of red blood cells during storage were focused mostly on 2,3-DPG. 2,3-DPG is a metabolite and allosteric modifier of haemoglobin and decreases quickly during the first 2 weeks of storage to almost undetectable levels. This decrease leads to an increase in haemoglobin oxygen affinity, which may be an explanation for the decrease of red-blood-cell oxygen-delivering ability during storage. However the 2,3-DPG levels appear to start to recover within several hours, and this may take up to 72 hours after transfusion *in vivo*.²² Considering the fact that blood transfusions are often given to acute patients, waiting for 2–3 days to see the effects of blood transfusion is hardly acceptable.

However, the clinical consequences of completely 2,3-DPG-depleted red-cell units do not seem to be that significant. Theoretically, if 2,3-DPG is not present in red blood cells stored longer than 2 weeks, then approximately two thirds or more of all stored red-cell units would be expected to be 2,3-DPG-depleted. In 2001 d'Almeida and colleagues, investigating the impact of 2,3-DPG depletion in an anaemic oxygen-supply-dependent rat model, compared fresh and old red blood cells stored for 7 days. They were not able to find any differences between the groups, and suggested that 2,3-DPG depletion has a minor physiological impact.²³ Additionally, a recent experimental study showed that although red blood cells were stored for 2–3 weeks and were completely devoid of 2,3-DPG, their oxygen-delivering capacity to the intestinal microcirculation in an oxygen-supply-dependent isovolaemic exchange model did not differ from that of fresh (2–6 days) red blood cells.²⁴ Therefore, we may conclude that decreases in 2,3-DPG levels are reversible and, in the view of storage damage, seem not to be too crucial.

Vasoactive compounds: ATP and NO

An additional biochemical change which occurs in stored red blood cells is the decrease in intracellular ATP levels. ATP, besides playing a secondary role in membrane deformability, is crucial for red-blood-cell function due to its central role in cellular metabolism as an energy source. Sugar transport into the red cell, protective anti-oxidant mechanisms, membrane phospholipid distribution, and all other functions are only possible if ATP is present or can be regenerated in the red blood cell. The newly discovered role of ATP as a vasodilator under hypoxic conditions has highlighted its importance for red-blood-cell function.

The mechanical and hypoxia-induced ATP release is believed to be through a specific membrane-bound receptor, the CFTR.⁹ This function probably depends on a number of factors, including the intracellular adenosine pool, red-cell cytoskeletal and membrane structure, and partially 2,3-DPG presence, in order to detect hypoxia.²⁵ Nevertheless, the complex regulation mechanism of oxygen-sensing and ATP-releasing functions is not very well understood and needs further studies. ATP depletion and the adenine pool in the red cell do not determine the red cell survival directly, but certainly have an important role in red-blood-cell function.

Raat et al²⁴ showed that ATP levels remained unchanged in red blood cells stored for 2–3 weeks, but dropped to 60% in red blood cells stored for 5–6 weeks. This finding was also associated with the oxygen-delivering ability of the red blood cells, and old (5–6 weeks' storage) red blood cells had a reduced oxygen-delivering capacity compared to fresh (2–6 days) and intermediate (2–3 weeks) ones. These findings support the idea that ATP may contribute to oxygen delivery by red blood cells due to its action as a vasodilator and its being released by red blood cells in the presence of hypoxia. This physiological property of ATP may be negatively affected by storage duration.

Another possible mechanism which may account for alterations in the oxygen-transporting capabilities of transfused red blood cells is their ability to generate nitric oxide under acidic and hypoxic conditions. Nitric oxide and its products, besides many other roles in the organisms, can be regarded as being among the major compounds accounting for vascular regulation due to their vasodilatory action on blood vessels. Recent studies have shown that red blood cells are able to release nitric oxide in the presence of hypoxia, and that this nitrite-mediated function accounts for hypoxia-induced vasodilation. An alternative route for hypoxia-induced nitric oxide has been proposed to be the presence of red blood cell-bound S-nitrosothiol.¹¹ The further identification of functional eNOS on red-blood-cell membranes has made the red cell a central player not only in oxygen transport but also in vascular control mechanisms. It could well be that this NO-mediated function of red blood cells may be affected during storage.

In conclusion, the current criteria for the quality of red blood cells for transfusions take biomechanical alterations into consideration as the basis for determining the in-vivo function of the cells. The major properties of blood which are routinely controlled are 0.8–1% haemolysis in stored units, 75% in-vivo survival within 24 hours after transfusions, and volume and haemoglobin content of red blood cells. These are indeed very useful quality parameters; however, biochemical alterations of red-blood-cell properties associated with vascular regulation as discussed above should also be taken into consideration. The alterations which occur during storage appear to be at least partially reversible by use of improved storage conditions, additional solutions, or rejuvenation. An important message in this context is the in-vivo recovery of 2,3-DPG and ATP levels within several hours up to a day after transfusions.

Preclinical and clinical studies

Fitzgerald and co-workers²⁶, using septic oxygen-supply-dependent rats, raised the question of whether the storage duration before transfusion has an impact on tissue oxygenation. The authors compared transfusion with old red blood cells stored in CPDA-1 for 28 days with fresh red blood cells stored for 3 days under oxygen supply conditions. They showed that the transfusion of old cells did not significantly improve the oxygen consumption (VO_2), whereas transfusion of fresh red blood cells acutely increased VO_2 .

Van Bommel et al²⁷, using a rat haemorrhagic shock model, compared the effects of resuscitation with fresh and old red blood cells, the latter stored for 28 days in CPD plasma, SAGM and CPDA-1 solutions. By measuring the intestinal microvascular PO_2 with O_2 -dependent quenching of palladium porphyrin phosphorescence technique, the authors were able to demonstrate that stored red blood cells did not restore the microcirculatory oxygenation, in contrast to fresh red blood cells; however, with the exception of the CPD-stored group, the storage damage was not severe enough to impair intestinal oxygen consumption.

However, d'Almeida et al²³ and Raat et al²⁴ indicate limitations in the previous types of rat models where stored rat red blood cells were used for transfusion. These limitations were the faster aging of rat red blood cells and failure of stored rat red blood cells to regenerate 2,3-DPG, unlike human red blood cells. Raat et al²⁴ developed a rat model able to accommodate human red-blood-cell transfusions. In a randomized controlled study on the ability of fresh (2–6 days), intermediate (2–3 weeks) and old (5–6 weeks) stored human red blood cells to improve gut microcirculatory oxygenation in anaemic oxygen-supply-dependent rats, the authors showed that oxygen delivery capacity was diminished in the old (5–6 weeks) group compared to the fresh and intermediate groups.

In conclusion, the preclinical studies demonstrated the harmful effects of prolonged storage on red-blood-cell functions. However, the results from clinical studies are confusing, and the answer to the question of how important these storage-induced alterations are in vivo, and especially in clinical conditions, remains uncertain.

Marik and Sibbald²⁸ were unable to show any beneficial effects of blood transfusion in septic patients, and Purdy and colleagues²⁹ showed, in severe septic patients, a relation between the age of transfused red blood cells and patient mortality. Keller et al found a relationship between the transfusion of red blood cells older than 14 days and length of hospital stay; however, they did not find a significant increase in length of intensive care stay. Recently Basran and colleagues³⁰ demonstrated that the mean storage duration of the transfused red blood cells was an independent predictor of in-hospital mortality, and associations were found between storage duration and length of hospital and intensive-care stay and acute renal dysfunction.

In contrast, Vamvakas and Carven³¹ could not find any deleterious effects in cardiac surgery patients of transfusion of aged cells. However, in a prospective double-blinded randomized study, Walsh et al³², using red blood cells stored for <5 days versus >20 days, did not observe any significant adverse effects in critically ill anaemic patients. Recently, Hebert et al investigated the effects in cardiac patients of a prolonged storage time of red blood cells used in transfusions. They designed two groups: the standard group received red-blood-cell units with an average storage time of 19 days, while the experimental group received red-blood-cell units with an average storage time of 4 days (5 and 3.4 units per patient, respectively). They found no difference in mortality

and morbidity between the two groups, despite a difference of 15 days in storage time. Van de Watering et al³³ studied 2732 patients who received buffy-coat-depleted red-blood-cell units. They compared patients who received red blood cells stored for longer than 18 days (median 24 days) to patients who received red blood cells stored for less than 18 days (median 13 days). They found no correlation between age of stored blood cells and patient outcome.

Similarly, in large prospective studies on both anaemia and blood transfusion in the critically ill^{34,35}, the storage time of the transfused blood was not associated with a higher mortality or morbidity. However, blood transfusion itself was independently associated with longer intensive-care and hospital stay and mortality.

Based on their findings, the authors above suggested that a limit of 18–28 days be used to identify a red-blood-cell unit as 'old'. If such a threshold were applied in clinical practice, what would the consequences be? To answer this, data on the storage duration of transfused red-blood-cell units are needed. Indeed, in recent large-population studies the storage times of transfused red blood cells were determined. In the Anemia and Blood Transfusion in the Critically Ill (ABC) study³⁴ the mean age of the blood was 16.2 days (± 7 days), whereas in the Current Clinical Practice in the United States (CRIT) study³⁵ the mean age of the blood was 21.2 (± 11.4 days). Interestingly age of blood was found not to be related to any clinical outcome. There was actually a trend, but this did not reach the significance level. However, in both of these studies the number of transfusions was relatively small (12,000 and 4000 respectively) in a total number of 16,000 units. In another study, Raat and his colleagues analysed the age of stored red-blood-cell concentrates in 74,084 units in the Academic Medical Centre in Amsterdam, the Netherlands, between the years 1997 and 2001, for a period of 5 years. They found that the mean storage time was 19.4 ± 7 days, with 37% older than 3 weeks.³⁶

The data above showed that, in a total of 90,000 red-blood-cell units, most of those being used in critically ill patients are 16–21 days old. One third of the patients received transfusions of blood older than 21 days, which supports the idea that dysfunction of these older cells may indeed be a clinical problem. However, while in-vitro studies were able to detect the storage-related changes, most preclinical studies have shown less beneficial, if not deleterious, effects of transfusions of stored red blood cells. One wonders why clinical studies produce such confusing results.

Several hypotheses can be proposed in order to explain this controversy. First of all very few studies have focused primarily on the impact of storage time on red blood cells. Those which did investigate the impact of storage did not monitor tissue oxygenation parameters as ultimate proof of the efficacy of blood transfusions, neither did they measure red-blood-cell properties, instead recording only general patient outcome variables such as mortality and morbidity. The results, therefore, do not allow evaluation of whether transfusion of red blood cells itself, the white-blood-cell burden, or other factors such as severity of disease or risks of transfusion might have caused these results. Under normal physiological conditions only a portion of oxygen delivered to the tissues is actually used. There is a residual capacity for increased demand, so that the tissues can continue to function even under extreme circumstances. Several studies have indeed shown that blood transfusions may increase the oxygen supply to the tissues; however, if oxygen consumption remains stable in patients without critical oxygen delivery status, its benefit would be questionable. Therefore, demonstration of the positive effects of blood transfusions should especially be seen in patients with critical oxygen supply where the compensatory mechanisms cannot handle the alterations in oxygen delivery. If the disease state is not severe in observed patients, this may mask the beneficial effects of blood transfusions.

White-blood-cell burden in stored red blood cells may be another factor affecting transfused blood function, since most studies have been performed prior to the implementation of leukocyte depletion. Several studies have shown the positive effect of leukocyte removal both *in vivo* and *in vitro*. Izbicki et al³⁷ have shown that storage for longer than 3 weeks may play an important role in the development of post-transfusional leukocytosis in transfusion of non-leukodepleted red blood cells by accumulation of interleukin 8. The cytokines and inflammatory mediators are known to be produced by white blood cells during blood storage, and these interfere with immune function. Therefore, theoretically, pre-storage leukoreduction should prevent the accumulation of these products.

Several studies have proposed a difference between the buffy-coat-depleted and leukodepleted red blood cell units.^{37–41} This was explained by the differences in the numbers of leukocytes achieved by these two methods. Buffy-coat-free red blood cells contain about 10^9 leukocytes per litre, whereas this number decreases to 10^6 in leukodepleted red-blood-cell units.

In support of this, Anniss and colleagues⁴² investigated the adherence of red blood cells to vascular endothelium, comparing non-leukodepleted, buffy-coat-poor and leukodepleted red-blood-cell units. They demonstrated significantly less adherence of leukodepleted cells on the first day of storage, and that adherence increased in all groups during 28 days of storage. After 28 days of storage both buffy-coat-poor and leukodepleted red-blood-cell units were less adherent than non-leukodepleted units. This finding supports the idea that white-blood-cell burden, besides causing transfusion-related alterations in immunological response and transfusion-related acute lung injury (TRALI), may worsen the storage-induced changes in the structure and function of the red blood cells.

Underlying diseases may interfere with these results. For instance, in septic patients, increased red cell destruction and shunting may possibly reduce the effects of blood transfusions. For example, Carroll and colleagues⁴³ demonstrated that red blood cells from diabetics had a decreased ATP-releasing ability which is probably associated with an altered antioxidant metabolism.

Another factor may be that the blood chosen to investigate the effects of prolonged storage in some studies may not be old enough, and the use of mixed red-blood-cell units with different storage times in clinical studies may mask the actual impact of storage time. Clinically relevant storage-induced red-blood-cell damage appears to become more obvious in red-blood-cell units which are stored for longer than 3 weeks, so it may be hypothesized that those stored for 18 days may actually be on the borderline. The proportion of these cells in circulation will probably contribute to the clinical efficacy of red blood cells. In clinical practice this can be translated as patients who receive more blood transfusions may be at higher risk, or conversely may benefit more, from this method, depending on how efficient the cells are.

Furthermore, the age of red blood cells at the time of collection may theoretically affect the impact of storage time on red blood cells. In normal physiological circumstances red blood cells have a life-span of approximately 120 days. Therefore a whole blood unit collected from a healthy donor will contain red blood cells with an age spectrum of 0–120 days. It is expected that a proportion of these cells should be older than average or approaching the end of their life span. These cells may undergo more storage-induced changes than younger cells. In support of this, Sparrow et al, in a very recent study, were able to separate young and old red blood cells prior to storage. They suggested a relationship between the age of the red blood cells at the time of blood donation, and changes in the cell-surface expression of cell adhesion molecules

and glycoporin A. Further research should focus on both biomechanical and biochemical alterations in red-blood-cell properties and their clinical importance. Better-designed studies using large populations and in-vivo tissue oxygenation techniques should be performed. The target groups for investigations should especially include patients in a critical oxygen delivery state.

Practice points

- in the absence of adequate evidence, advice to use fresh red blood cells in all patients is unrealistic and unnecessary. Accumulating in-vitro and experimental data, however, strongly suggest the use of fresh red blood cells, especially in critically ill patients who are in an oxygen-supply-dependent state. In such patients, if transfusion is needed, the transfusion of fresh red blood cells may be advised. However, the question regarding relatively old cells still needs to be investigated
- patients' own blood is preferable to stored blood, and therefore the first aim should be to prevent blood loss in patients. Good bleeding control, cell salvage, and avoidance of unnecessary blood sampling for medical reasons may decrease anaemia in most patients. Allogeneic blood transfusion alternatives can be used in some patients
- studies have shown that restrictive blood transfusion triggers may be better for patients. This is supported by most recent guidelines. In practice, if haemoglobin values are >10 g/dL blood transfusions are generally not given, and if <6 g/dL most patients are given at least one blood transfusion. However, decisions on transfusion for patients with a haemoglobin value between these limits should be made individually by the clinicians. The use of haematocrit and systemic haemoglobin values may give a general idea about tissue oxygenation, but they are not the best methods for deciding whether to transfuse because of individual differences between patients in their tolerance of anaemia. Physiological transfusion triggers may be used to evaluate organ function, such as ST elevations observed in electrocardiograms.. However, it should be taken into consideration that each organ has a different residual capacity and may respond differently
- flow redistribution may affect the response to blood transfusions in critically ill patients. Therefore in-vivo monitoring of tissue oxygenation at the bedside is essential. The lack of in-vivo monitoring techniques was a limiting factor in such studies, and can account for why the findings in in-vitro and preclinical studies could not be confirmed in clinical studies. However, these techniques are now available, and some studies have been performed observing microcirculation after blood transfusions. Several patient groups are of particular interest here, such as those undergoing cardiac surgery and extracorporeal circulation, septic patients, haematological diseases and oncology patients. In these diseases, microcirculatory disturbance is caused by different mechanisms, and understanding these changes may improve our understanding of oxygen delivery in critically ill patients
- it appears to be important to revise and standardize the quality criteria for red blood cells by including functional biochemical properties in addition to current regulations based on haemolysis and haemoglobin mass

ACKNOWLEDGEMENTS

Emre Almac is supported by a grant from the Leindsteiner Foundation for Blood Transfusion (LSBR) research grant nr. 0629.

REFERENCES

1. Cabrales P & Tsai AG. Plasma viscosity regulates systemic and microvascular perfusion during acute extreme anemic conditions. *American Journal of Physiology. Heart and Circulatory* 2006; **291**(5): H2445–H2452.
2. Cabrales P, Martini J, Intaglietta M & Tsai AG. Blood viscosity maintains microvascular conditions during normovolemic anemia independent of blood oxygen-carrying capacity. *American Journal of Physiology. Heart and Circulatory* 2006; **291**(2): H581–H590.
3. Shonat RD & Johnson PC. Oxygen tension gradients and heterogeneity in venous microcirculation: a phosphorescence quenching study. *The American Journal of Physiology* 1997; **272**(5 Pt 2): H2233–H2240.
4. Ellsworth ML. The red blood cell as an oxygen sensor: what is the evidence? *Acta Physiologica Scandinavica* 2000; **168**(4): 551–559 [Review].
5. Dietrich HH, Ellsworth ML, Sprague RS & Dacey Jr RG. Red blood cell regulation of microvascular tone through adenosine triphosphate. *American Journal of Physiology. Heart and Circulatory* 2000; **278**(4): H1294–H1298.
6. Crawford JH, Isbell TS, Huang Z et al. Hypoxia, red blood cells, and nitrite regulate NO-dependent hypoxic vasodilation. *Blood* 2006; **107**(2): 566–574.
7. Cosby K, Partovi KS, Crawford JH et al. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. *Nature Medicine* 2003; **9**(12): 1498–1505.
- *8. Kleinbongard P, Schulz R, Rassaf T et al. Red blood cells express a functional endothelial nitric oxide synthase. *Blood* 2006; **107**(7): 2943–2951.
9. Sprague RS, Ellsworth ML, Stephenson AH et al. Deformation-induced ATP release from red blood cells requires CFTR activity. *The American Journal of Physiology* 1998; **275**(5 Pt 2): H1726–H1732.
10. Jagger JE, Bateman RM, Ellsworth ML & Ellis CG. Role of erythrocyte in regulating local O₂ delivery mediated by hemoglobin oxygenation. *American Journal of Physiology. Heart and Circulatory* 2001; **280**(6): H2833–H2839.
11. Jia L, Bonaventura C, Bonaventura J & Stamler JS. S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control. *Nature* 1996; **380**: 221–226.
12. Schechter AN & Gladwin MT. Hemoglobin and the paracrine and endocrine functions of nitric oxide. *The New England Journal of Medicine* 2003; **348**: 1483–1485.
13. Wolfe LC. The membrane and the lesions of storage in preserved red cells. *Transfusion* 1985; **25**(3): 185–203 [Review].
14. Card RT. Red cell membrane changes during storage. *Transfusion Medicine Reviews* 1988; **2**: 40–47.
15. Hess JR & Greenwalt TJ. Storage of red blood cells: New approaches. *Transfusion Medicine Reviews* 2002; **16**: 283–295.
16. Rumsby MG, Trotter J, Allan D & Michell RH. Recovery of membrane micro-vesicles from human erythrocytes stored for transfusion: a mechanism for the erythrocyte discocyte-to-spherocyte shape transformation. *Biochemical Society Transactions* 1977; **5**(1): 126–128.
17. Brunauer LS, Moxness MS & Huestis WH. Hydrogen peroxide oxidation induces the transfer of phospholipids from the membrane into the cytosol of human erythrocytes. *Biochemistry* 1994; **33**(15): 4527–4532.
- *18. Verhoeven AJ, Hilarius PM, Dekkers DW et al. Prolonged storage of red blood cells affects aminophospholipid translocase activity. *Vox Sanguinis* 2006; **91**(3): 244–251.
- *19. Sparrow RL, Healey G, Patton KA & Veale MF. Red blood cell age determines the impact of storage and leukocyte burden on cell adhesion molecules, glycophorin A and the release of annexin V. *Transfusion and Apheresis Science* 2006 Feb; **34**(1): 15–23.
20. Annis AM & Sparrow RL. Expression of CD47 (integrin-associated protein) decreases on red blood cells during storage. *Transfusion and Apheresis Science* 2002 Dec; **27**(3): 233–238.

21. Bessos H & Seghatchian J. Red cell storage lesion: the potential impact of storage-induced CD47 decline on immunomodulation and the survival of leucofiltered red cells. *Transfusion and Apheresis Science* 2005 Apr; **32**(2): 227–232.
22. Heaton A, Keegan T & Holme S. In vivo regeneration of red cell 2,3-diphosphoglycerate following transfusion of DPG-depleted AS-1, AS-3 and CPDA-1 red cells. *British Journal of Haematology* 1989; **71**(1): 131–136.
- *23. d'Almeida MS, Gray D, Martin C et al. Effect of prophylactic transfusion of stored red blood cells on oxygen reserve in response to acute isovolemic hemorrhage in a rodent model. *Transfusion* 2001 Jul; **41**(7): 950–956.
- *24. Raat NJ, Verhoeven AJ, Mik EG et al. The effect of storage time of human red cells on intestinal micro-circulatory oxygenation in a rat isovolemic exchange model. *Critical Care Medicine* 2005; **33**(1): 39–45 [discussion 238–239].
25. Hamasaki N & Yamamoto M. Red blood cell function and blood storage. *Vox Sanguinis* 2000; **79**(4): 191–197 [Review].
26. Fitzgerald RD, Martin CM, Dietz GE et al. Transfusing red blood cells stored in citrate phosphate dextrose adenine-1 for 28 days fails to improve tissue oxygenation in rats. *Critical Care Medicine* 1997; **25**(5): 726–732.
27. van Bommel J, de Korte D, Lind A et al. The effect of the transfusion of stored red blood cells on intestinal microvascular oxygenation in the rat. *Transfusion* 2001; **41**(12): 1515–1523.
28. Marik PE & Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA: The Journal of the American Medical Association* 1993; **269**: 3024–3029.
29. Purdy FR, Tweeddale MG & Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Canadian Journal of Anaesthesia* 1997; **44**(12): 1256–1261.
30. Basran S, Frumento RJ, Cohen A et al. The association between duration of storage of transfused red blood cells and morbidity and mortality after reoperative cardiac surgery. *Anesthesia and Analgesia* 2006 Jul; **103**(1): 15–20.
31. Vamvakas EC & Carven JH. Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. *Transfusion* 2000; **40**: 101–109.
32. Walsh TS, McArdle F, McLellan SA et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Critical Care Medicine* 2004; **32**: 364–371.
- *33. van de Watering L, Lorinser J, Versteegh M et al. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. *Transfusion* 2006; **46**(10): 1712–1718.
34. Corwin HL, Gettinger A, Pearl RG et al. The CRIT Study: anemia and blood transfusion in the critically ill — current clinical practice in the United States. *Critical Care Medicine* 2004; **32**: 39–52.
35. Vincent JL, Baron JF, Reinhart K et al. Anemia and blood transfusion in critically ill patients. *JAMA: The Journal of the American Medical Association* 2002; **288**: 1499–1507.
- *36. Raat NJ, Berends F, Verhoeven AJ et al. The age of stored red blood cell concentrates at the time of transfusion. *Transfusion Medicine (Oxford, England)* 2005; **15**(5): 419–423.
37. Izbicki G, Rudensky B, Na'amad M et al. Transfusion-related leukocytosis in critically ill patients. *Critical Care Medicine* 2004; **32**(2): 439–442.
38. Bilgin YM, van de Watering LM, Eijsman L et al. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. *Circulation* 2004; **109**(22): 2755–2760.
39. Fung MK, Rao N, Rice J et al. Leukoreduction in the setting of open heart surgery: A prospective cohort-controlled study. *Transfusion* 2004; **44**: 30–35.
- *40. Fung MK, Moore K, Ridenour M et al. Clinical effects of reverting from leukoreduced to nonleukoreduced blood in cardiac surgery. *Transfusion* 2006; **46**(3): 386–391.
41. van de Watering LM, Hermans J, Houbiers JG et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. *Circulation* 1998; **97**(6): 562–568.
- *42. Anniss AM & Sparrow RL. Storage duration and white blood cell content of red blood cell (red blood cell) products increases adhesion of stored red blood cells to endothelium under flow conditions. *Transfusion* 2006; **46**(9): 1561–1567.
- *43. Carroll J, Raththagala M, Subasinghe W et al. An altered oxidant defense system in red blood cells affects their ability to release nitric oxide-stimulating ATP. *Molecular BioSystems* 2006; **2**(6-7): 305–311.

Alternatives to allogeneic blood transfusions

Andreas Pape*

Dr. med.

*Clinic of Anaesthesiology, Intensive Care Medicine and Pain Management, J. W. Goethe University
Hospital Frankfurt am Main, Theodor Stern Kai 7, 60590 Frankfurt am Main, Germany*

Oliver Habler

Professor Dr. med. Department Head

*Clinic of Anaesthesiology, Surgical Intensive Care Medicine and Pain Management,
Nordwest-Krankenhaus, Steinbacher Hohl 2-26, 60488 Frankfurt am Main Germany*

Inherent risks and increasing costs of allogeneic transfusions underline the socioeconomic relevance of safe and effective alternatives to banked blood. The safety limits of a restrictive transfusion policy are given by a patient's individual tolerance of acute normovolaemic anaemia. Iatrogenic attempts to increase tolerance of anaemia are helpful in avoiding premature blood transfusions while at the same time maintaining adequate tissue oxygenation. Autologous transfusion techniques include preoperative autologous blood donation (PAD), acute normovolaemic haemodilution (ANH), and intraoperative cell salvage (ICS). The efficacy of PAD and ANH can be augmented by supplemental iron and/or erythropoietin. PAD is only cost-effective when based on a meticulous donation/transfusion plan calculated for the individual patient, and still carries the risk of mistransfusion (clerical error). In contrast, ANH has almost no risks and is more cost-effective. A significant reduction in allogeneic blood transfusions can also be achieved by ICS. Currently, some controversy regarding contraindications of ICS needs to be resolved. Artificial oxygen carriers based on perfluorocarbon (PFC) or haemoglobin (haemoglobin-based oxygen carriers, HBOCs) are attractive alternatives to allogeneic red blood cells. Nevertheless, to date no artificial oxygen carrier is available for routine clinical use, and further studies are needed to show the safety and efficacy of these substances.

Key words: blood; transfusion; alternatives; anaemia tolerance; donation; haemodilution; cell salvage; artificial O₂ carriers; blood substitutes.

* Corresponding author. Tel.: +49 69 6301 83627; Fax: +49 69 6301 83768.
E-mail address: a.pape@em.uni-frankfurt.de (A. Pape).

Table 1. Incidences of potential risks associated with allogeneic blood transfusions.

Risk factor	Incidence	
Mistransfusion	Acute haemolytic reaction	1:6000–1:33,000
	Delayed haemolytic reaction	1:2000–1:11,000
Infections (viral)	HIV	1:20 million
	Hepatitis A	1:1 million
	Hepatitis B	1:63,000–1:320,000
	Hepatitis C	1:1.2–1:11 million
	Cytomegalovirus (CMV)	1:10–1:30
	Epstein–Barr virus (EBV)	1:200
Infections (Bacterial)	<i>Yersinia enterocolica</i> , <i>Serratia marcescens</i> , <i>Pseudomonas</i> , enterobacteria	1:200,000–1:4.8 million
	Immunological	
	Transfusion-related lung injury (TRALI)	1:4000
	Alloimmunization	1:16,000
	Immunosuppression	1:1
	Allergic transfusion reaction	1:2000

Although safer than ever before, the transfusion of allogeneic blood is still associated with risks for the recipient (cf. Table 1), the most serious of which are allergic reactions, transfusion-related lung-injury (TRALI), accidental mistransfusions ('clerical error'), and the transmission of viral and bacterial infections (hepatitis, HIV, cytomegalovirus, Epstein–Barr virus).^{1,2} Indeed, the results of several prospective clinical studies indicate that a restrictive transfusion regimen is associated with lower morbidity and mortality than a liberal transfusion policy.^{3–7}

Moreover, public health systems are facing a cost explosion resulting from transfusion-related morbidity as well as from continuously rising costs of the blood products themselves; because of the growing imbalance between the decreasing rate of blood donation and the continuously increasing demand, the costs of blood products are expected to double until 2030.^{8,9}

To control both the inherent risks as well as the increasing costs, allogeneic blood transfusions should be either completely avoided or at least reduced to an absolute minimum during surgical procedures.

This chapter reviews the following topics in connection with alternatives to allogeneic blood transfusions: (1) the tolerance of acute normovolaemic anaemia, including the acceptance of low intraoperative haemoglobin (Hb) concentrations; (2) the employment of autologous transfusion techniques, including supportive administration of erythropoietin; and (3) the potential of artificial oxygen carriers as substitutes for allogeneic red blood cells (RBCs).

TOLERANCE OF ACUTE NORMOVOLAEMIC ANAEMIA

The initial treatment of intraoperative blood loss always consists in the maintenance of normovolaemia by the infusion of crystalloid (3:1) and colloidal solutions (1:1). This acellular fluid replacement implies the dilution of the cell mass remaining in the vasculature (haemodilution), resulting in a dilutional anaemia (acute normovolaemic anaemia).

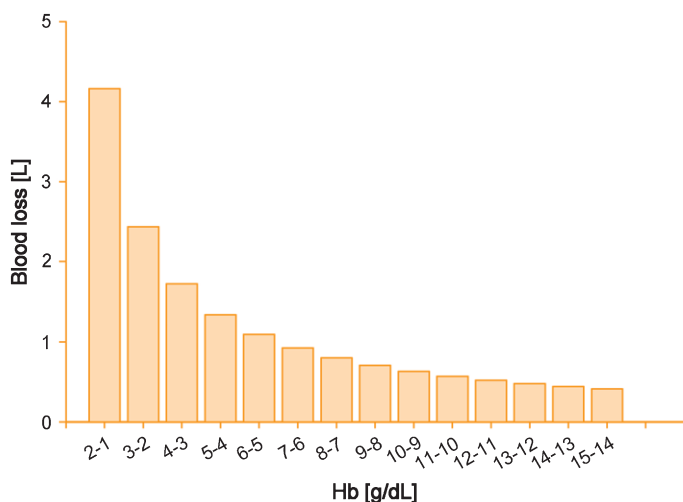


Figure 1. Extent of normovolaemic exchange of blood for acellular fluids necessary to decrease haemoglobin by 1 g/dL, exemplarily calculated for a man (body weight 80 kg, height 1.8 m, blood volume 6000 mL). X-axis: stepwise decrease in haemoglobin concentration by 1 g/dL. Y-axis: blood loss necessary to realize the respective drop in haemoglobin by maintenance of normovolaemia with cell-free solutions during acute blood loss. The lower the starting haemoglobin, the greater the blood loss necessary to decrease the haemoglobin concentration by 1 g/dL.

In the context of alternatives to allogeneic blood transfusion, the term ‘anaemia tolerance’ is used to refer to the patient’s physiological ability to tolerate acute normovolaemic anaemia as well as the anaesthesiologist’s intention to accept low haemoglobin concentrations. Hence, the omission of any avoidable transfusion represents the simplest but also the most important alternative to allogeneic blood transfusion. Indeed, the acceptance of low haemoglobin values offers two incentives: (1) the more diluted the patient – i.e. the lower the intravascular haemoglobin concentration – the less the red cell mass lost/mL blood loss (Figure 1); and (2) postponing the transfusion until after surgical haemostasis has been achieved increases the percentage of transfused red blood cells which remain within the vasculature rather than being spilled out with uncontrolled blood loss.

Compensatory mechanisms of dilutional anaemia

Regardless of the fact that arterial oxygen content (CaO_2) decreases proportionally with haematocrit (Hct), it has been known for a long time that normal oxygen supply and tissue oxygenation do not depend on a normal haemoglobin concentration, always presuming that normovolaemia is maintained.^{10,11}

Initially, dilutional anaemia is essentially compensated by an increase in cardiac output (CO), which at first is caused exclusively by an increase in left ventricular stroke volume. In more profound stages of normovolaemic anaemia, this is accompanied by an increase in heart rate (HR). Oxygen delivery to the tissues (DO_2) begins to decrease beyond baseline level at Hct values lower than $\sim 25\%$, so that haemodilution

to Hct $\sim 25\%$ (corresponding to a haemoglobin concentration of ~ 8 g/dL) occurs without a net decrease in DO_2 .

At Hct values below $\sim 25\%$, the compensation for dilutional anaemia via CO increase becomes exhausted, and DO_2 starts to fall below the baseline level. To maintain tissue oxygen demand – as reflected by total body oxygen consumption (VO_2) – the decreasing DO_2 is further compensated by: (1) utilization of ‘luxury DO_2 ’ (under normal conditions, DO_2 exceeds VO_2 by a factor of 3–4); (2) a haemodilution-related increase in nutritive organ blood flow; (3) homogenization of local DO_2 ; and (4) an increase in tissue oxygen extraction.¹² Therefore, VO_2 initially remains unchanged despite falling DO_2 (oxygen-supply-independency of VO_2 , see Figure 2a).

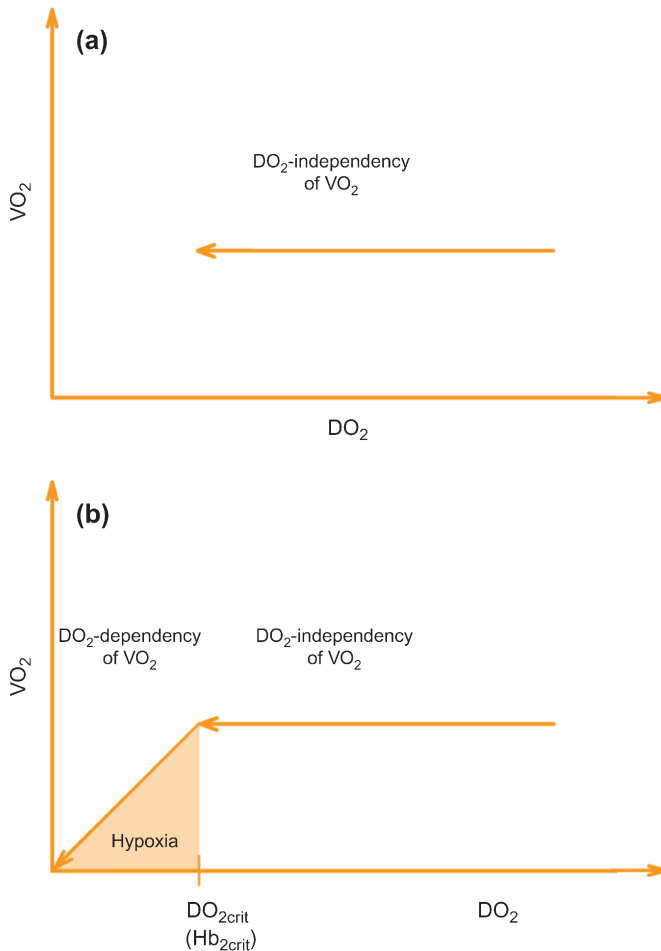


Figure 2. The relationship between oxygen consumption (VO_2) and oxygen delivery (DO_2). Physiologically, DO_2 is three or four times higher than VO_2 . (a) Over a long period, VO_2 remains independent of DO_2 despite the anaemia-related decrease of DO_2 (oxygen-supply-independency of DO_2). (b) When a critical haemoglobin concentration (Hb_{crit}) is reached, DO_2 falls short of the actual oxygen demand and VO_2 begins to decrease (onset of oxygen-supply-dependency of VO_2).

Limits of dilutional anaemia – the concept of critical Hct

At extreme degrees of dilutional anaemia, DO_2 falls below a critical value (DO_{2crit}). The amount of oxygen delivered to the tissues becomes insufficient to meet their oxygen demand, and VO_2 starts to decline (oxygen-supply-dependency of VO_2 , cf. Figure 2b).¹³ This indirectly indicates the onset of tissue hypoxia. The haemoglobin value that corresponds to the inflection of VO_2 is called ‘critical haemoglobin’ (Hb_{crit}) and reflects the physiological limit of dilutional anaemia. In a standardized experimental protocol, it could be demonstrated that the persistence of DO_{2crit} without any treatment finally leads to death in less than 3 hours.¹⁴

Both DO_{2crit} and Hb_{crit} vary within and between individuals and are influenced by different physiological circumstances (see below). In previous experimental studies, Hb_{crit} values between 2 and 3 g/dL were found. In clinical observations in anaesthetized patients, extremely low haemoglobin concentrations (3.0 ± 0.8 g/dL in children undergoing major spine surgery¹⁵ and 1.1 g/dL in an unexpected massive blood loss¹⁶) have been tolerated without meeting the DO_{2crit} (Table 2).

Table 2. Physiological limits of acute normovolaemic anaemia in different species.

Author	Species	Anaesthesia	FiO_2	Plasma substitute	Identification of Hb_{crit}	Hb_{crit} (g/dL)
Fontana et al ¹⁵	Man (child)	Isoflurane Sufentanil Vecuronium	1.0	Albumin	Decay of VO_2	2.1
Van Woerkens et al ⁹⁹	Man (84 years)	Enflurane Fentanyl Pancuronium	0.4	Gelatin	Decay of VO_2	4
Zollinger et al ¹⁶	Man (58 years)	Propofol Fentanyl Pancuronium	1.0	Gelatin	ST-segment depression	~ 1.1
Cain et al ¹³	Dog	Pentobarbital	0.21	Dextran	Decay of VO_2	3.3
Meier et al ¹⁴	Pig	Propofol Fentanyl	0.21	HES	Decay of VO_2	3.1 ± 0.4
Pape et al ²⁴	Pig	Propofol Fentanyl Midazolam Pancuronium	0.6	HES	Decay of VO_2	1.5 ± 0.4
Kemming et al ¹⁰⁰	Pig	Midazolam Morphine Pancuronium	0.21	HES	ST-segment depression	2.6 ± 0.3
Meisner et al ¹⁰¹	Pig	Diazepam Morphine Pancuronium	0.21	Albumin	ST-segment depression	2.0 ± 0.8
Meier et al (unpublished data)	Pig	Propofol Fentanyl Pancuronium	0.21	HES	Decay of VO_2	2.6 ± 0.4

Hb_{crit} , critical haemoglobin level; HES, hydroxyethyl starch.

These data demonstrate that the tolerance of acute normovolaemic anaemia is high in anaesthetized subjects. However, the presented concept of DO_{2crit} refers to a critical limitation of total body oxygen supply. The limiting factor of anaemia tolerance is the oxygenation of the myocardium as the motor of haemodynamic compensation: when DO_{2crit} is reached, a deterioration in myocardial performance represents imminent breakdown of total body oxygenation.

Since myocardial oxygen extraction is already maximal under rest conditions, increased myocardial oxygen demands can only be met by utilization of the coronary flow reserve.¹⁷ In contrast, other vitally important organs (i.e. brain, intestine, kidneys) can increase oxygen extraction to compensate for acute anaemia.¹⁸ However, what degree of dilutional anaemia may result in a critical limitation of oxygen delivery to these organs has not yet been completely elucidated. Further research is necessary to identify organ-specific limits of anaemia tolerance.

Factors influencing anaemia tolerance

DO_{2crit} and Hct_{crit} are influenced by a couple of physiological variables. The basic requirement for the efficacious compensation of dilutional anaemia is normovolaemia. During hypovolaemic haemodilution the total body oxygen demand increases due to the release of catecholamines and other stress hormones, and the 'critical' oxygen delivery (DO_{2crit}) is met at higher values than under normovolaemia. Myocardial performance is another variable that determines anaemia tolerance. During haemodynamic compensation of dilutional anaemia, increased myocardial oxygen demand is met by a coronary vasodilation and an increase in coronary blood flow (coronary flow reserve, see above). In patients with restricted coronary reserve (e.g. coronary artery disease), limited ventricular performance (e.g. congestive heart failure) and cardiodepressive medication, anaemia tolerance is reduced.¹⁹

Anaemia tolerance is also influenced by the depth of anaesthesia and muscular relaxation. In high doses most of the anaesthetics attenuate the cardiac output response during haemodilution and thus reduce anaemia tolerance.²⁰ In contrast, neuromuscular blockade increases anaemia tolerance, since skeletal muscle mass represents about 30% of total body mass, so that reduction in muscular oxygen demand significantly decreases total body oxygen consumption.²¹ In an experimental study in anaesthetized pigs, deep neuromuscular block using rocuronium significantly increased anaemia tolerance (Hb_{crit} 2.4 ± 0.5 g/dL versus 3.2 ± 0.7 g/dL in animals without relaxation; personal unpublished data).

Moreover, body temperature modulates anaemia tolerance. In experimental models mild hypothermia has been shown to increase anaemia tolerance due to a reduction in total body oxygen demand.²² The opposite should be postulated for hyperthermia.

Finally, anaemia tolerance can also be increased by ventilation with high inspiratory oxygen fraction (FiO_2 , hyperoxic ventilation). The amount of oxygen physically dissolved in the plasma increases proportionally with arterial partial pressure of oxygen (paO_2). In profound anaemia, the plasma compartment is significantly increased and becomes an important source of oxygen.²³ In experimental studies, the positive effect of hyperoxic ventilation on anaemia tolerance has been demonstrated repeatedly (Table 3).^{14,24-26}

The omission of any avoidable transfusion is the most important alternative to the application of allogeneic blood. In the best case, permissive anaemia can be sustained

Table 3. Factors influencing anaemia tolerance.

Factor	Effect on anaemia tolerance
Hypovolaemia	↓
Coronary arterial stenosis	↓
Hyperoxaemia	↑
Muscular relaxation	↑
Hypothermia	↑
Depth of anaesthesia	↓
Choice of infusion fluid	↔
Hypoxaemia	↔
Sepsis	↓
Polytrauma	↓
Pregnancy	↔
Chronic anaemia	↔

until surgical bleeding is under control²⁷, which may allow saving of blood products which would get lost immediately after transfusion via the ongoing bleeding. The patient's individual tolerance towards acute normovolaemic anaemia reflects the margin of safety, in between which any restrictive transfusion policy will not be associated with an increased the risk of tissue hypoxia. Both the optimization of anaemia tolerance and the choice of an adequate transfusion trigger (cf. Chapter 2 by B. Vallet) enable the implementation of a safe and effective blood-sparing strategy.

AUTOLOGOUS TRANSFUSION TECHNIQUES

Autologous transfusion techniques are generally intended to replace as many allogeneic RBC transfusions as possible by (re)transfusion of autologous blood. Autologous blood is either harvested a couple of weeks before (preoperative blood donation, PAD) or immediately before surgery (acute normovolaemic haemodilution, ANH). The concept of intraoperative cell salvage (ICS) implies the collection and reprocessing of shed blood for autologous retransfusion.

Preoperative autologous blood donation (PAD)

In the course of PAD, autologous whole blood is collected weekly within 4–6 weeks prior to surgery. The final donation must not be performed later than 72 hours before surgery.²⁸ Whole blood units are separated into red blood cells and plasma, and subsequently classified according to the ABO and rhesus systems and clearly allocated to the donor.

Usually, PAD is suitable when a blood loss of 500–1000 mL is anticipated in at least 5–10% of the cases, or when the estimated transfusion probability exceeds 50%, respectively. The minimum acceptable haemoglobin concentration for PAD is 11 g/dL.²⁸ In the presence of lower preoperative haemoglobin levels the supportive administration of iron and/or recombinant erythropoietin (rhEPO) may encourage PAD anyway (see below).

PAD is contraindicated in patients with elevated cardiac risk, i.e., patients with unstable angina, myocardial infarction within the previous 3 months, coronary artery

main stem stenosis, congestive heart failure, and significant aortic valve stenosis (gradient >70 mmHg).²⁹

The adequate number of PAD units has to be calculated prospectively for each individual case, the type of surgery, the probability of a transfusion requirement, and the time left until the date of surgery being taken into consideration. A helpful tool may be the maximum surgical blood ordering schedule (MSBOS), which is based on a specific institutional analysis of the mean number of blood units transfused per type of surgical intervention and individual surgeon.^{30,31}

The cost-efficacy of PAD decreases with the number of blood units discarded¹¹, which underlines the necessity to exactly calculate the individual number of blood donations.³² Indeed, PAD is not cost-effective if only one unit of allogeneic blood must be transfused despite previous PAD, or if more than 15% of donated blood is discarded.³³

Major risks associated with PAD consist in contamination during storage and – as in the transfusion of allogeneic blood – in the potential clerical error with consecutive mistransfusion.³⁴

Whereas the blood-sparing potential of PAD had been documented in some previous studies²⁹, a recent meta-analysis indicates that PAD is actually associated with a higher overall transfusion rate.³⁵ Overall it can be assumed that other blood-conservation techniques will increasingly replace PAD in elective surgical procedures.

Acute normovolaemic haemodilution (ANH)

ANH entails the isovolumic exchange of whole blood for acellular fluids (colloids and/or crystalloids) directly prior to surgery.³⁶ Usually, 3–4 units of blood are withdrawn and are stored at the bedside in the operating room. In terms of the safe application of ANH, it is essential to know the physiological changes that occur during dilutional anaemia (see above), and to evaluate the patient's individual anaemia tolerance (i.e. the lowest, safely tolerable haemoglobin level).³⁷ The benefit of ANH consists in a reduction of net RBC loss related to dilutional anaemia (see above) and the availability of fresh whole blood, including coagulatory factors and platelets, for autologous retransfusion.

The blood-sparing efficacy of ANH depends on the baseline haemoglobin level, the target haemoglobin after ANH, and the dimension of blood loss measured as a fraction of circulating blood volume.³⁸ ANH should therefore target as low a haemoglobin concentration as possible while still leaving an adequate margin of safety for tissue oxygenation (i.e. haemoglobin 6–7 g/dL in otherwise healthy patients and 9–10 6–7 g/dL in patients with cardiovascular comorbidity).

While the efficacy of ANH in reducing perioperative allogeneic transfusion could be demonstrated in several clinical trials (abdominal, vascular, orthopaedic, urological and maxillofacial surgery)^{39–43}, the same effect could not be confirmed in some meta-analyses.^{44,45} However, the heterogeneity of transfusion managements between different institutions (e.g. choice of transfusion triggers) complicates the comparability of the different patient populations.

ANH is contraindicated with unstable angina, coronary artery disease with significant main-stem stenosis or myocardial infarction within the past 6 months, high-grade aortic valve and carotid artery stenosis, renal insufficiency, and manifest bacteraemia, but not with malignant disease.

All in all, ANH should be preferred to PAD, since: (1) ANH is less expensive than PAD (\$28 versus \$226 per unit)⁴⁶ because travel expenses, costs for staff, material,

and processing and testing devices can be omitted; and (2) the performance of ANH allows for a more flexible scheduling of the date of surgery since the complex logistics necessary for PAD can be omitted. As a blood conservation method, ANH has been readopted in the practice guideline for perioperative blood transfusion of the American Society of Anesthesiologists (ASA).⁴⁷

Supportive administration of iron and/or recombinant human erythropoietin (rhEPO)

During the perioperative phase, iron and/or rhEPO are administered either alone⁴⁸ or in combination with PAD and/or ANH¹¹, both allowing for the implementation of a restrictive transfusion protocol. In particular, anaemic patients seem to benefit from preoperative substitution of iron⁴⁸, whereas in non-anaemic patients undergoing orthopaedic surgery the isolated administration of iron did not decrease the perioperative transfusion rate.⁴⁹ In combination with PAD, the substitution of iron (e.g. 100–200 mg/day orally) is recommended anyway for treatment of PAD-related anaemia.²⁹

The administration of rhEPO (e.g. 100–150 U/kg subcutaneously twice a week) should always be accompanied by iron substitution in order to achieve an effective stimulation of erythropoiesis.⁵⁰ In these low dosages, the costs of rhEPO are comparable with those of allogeneic blood.⁵¹ The augmentation of haematopoiesis alone has already been proven to reduce allogeneic blood transfusions, since a low preoperative haemoglobin level is a relevant predictor of allogeneic RBC transfusion.¹¹ Moreover, an increase in preoperative haemoglobin levels using rhEPO also increases the efficacy of ANH by allowing for a more extensive exchange of blood for acellular fluids.

Intraoperative cell salvage (ICS)

In surgical interventions with a blood loss of at least 800–1000 mL, autotransfusion of RBCs salvaged from shed blood is a highly effective method for reducing allogeneic blood transfusions. Basically, shed blood is aspirated via a heparinized suction tube into a collection reservoir. Erythrocytes are salvaged by differential centrifugation and washing in 0.9% saline, while contaminants such as fibrin, cell debris, microaggregates, bone fragments, fat, haemoglobin and heparin are eliminated. Depending on the washing program, the haematocrit of the autologous RBC concentrate is 55–80%.⁵² The quality of salvaged blood is excellent compared with stored pRBCs; fresh salvaged blood has a lower oxygen affinity related to a more physiological pH and a higher content of ATP and 2,3-diphosphoglycerate (2,3-DPG). However, an extensive list of contraindications to ICS is traditionally proposed by the manufacturers of ICS devices (Table 4).

To a certain extent, these contraindications have been challenged by recent literature. Only the potential bacterial contamination of collected wound blood represents an absolute contraindication for autotransfusion in patients undergoing replacement surgery (i.e., implantation of vascular grafts or joint prostheses, cardiac valve replacement).³³

In the case of definite contamination of shed blood with bacteria or malignant cells, some authors advocate the use of PAL leukocyte-depleting filters in addition to the centrifugation and washing process of the cell saver.⁵³ A recent study performed in a South African trauma centre even suggests that ICS without PAL filters in 44 patients with penetrating abdominal trauma significantly reduced the need for allogeneic blood

Table 4. Proposed contraindications to intraoperative cell salvage.

Pharmacological agents	Clotting agents Irrigating solutions meant for topical use Methylmethacrylate
Contaminants	Urine Bone chips Fat Bowel contents Infection Amniotic fluid
Malignancy	
Haematological disorders	Sickle-cell disease Thalassaemia
Miscellaneous	Carbon monoxide (electrocautery smoke) Catecholamines (phaeochromocytoma) Oxymetazoline

From Waters (2004, *Transfusion* 44: 40S–44S) with permission.

transfusions. These patients received prophylactic antibiotics, and no differences to the control group were apparent regarding the incidence of sepsis or overall mortality.⁵⁴

As a highly effective method for completely eliminating contaminating tumour cells, Hansen and co-workers propose the irradiation of RBC concentrates salvaged from operating fields in cancer surgery.⁵⁵ Moreover, irradiation of salvaged blood has been demonstrated to mitigate the release of inflammatory mediators, which may provide an additional advantage when compared with allogeneic blood.⁵⁶

Even in obstetric surgery, ICS seems possible when combined with PAL leukocyte filters.⁵⁷ A current investigation demonstrated that these filters effectively removed squamous cells and other amniotic contaminants from washed blood salvaged during caesarean deliveries.⁵⁸ However, in the setting of a massive blood loss, the efficacy of this procedure seems questionable, since the filter interposed into the transfusion line increases the resistance of the system, resulting in a substantial reduction in transfusion velocity.

In any case, it must be borne in mind that any use of cell salvage, despite the stipulated contraindications, represents off-label use from the medico-legal point of view, and has to be based on a thorough analysis of the individual risk/benefit ratio. Further systematic research is necessary to elucidate important safety aspects of these application modalities.

The blood-sparing potential of ICS has been proven in several clinical trials and meta-analyses.^{11,35,59} ICS is also accepted by Jehovah's Witnesses as long as the patient, collection system, processing unit and final blood bag form a closed circuit.⁶⁰

ARTIFICIAL OXYGEN CARRIERS

An attractive alternative to allogeneic RBCs consists in synthetic blood substitutes (artificial oxygen carriers), which can be applied independently of blood-group typing or infectious risks. Currently, there are two types of artificial oxygen carrier under experimental and clinical investigation: (1) synthetically manufactured perfluorocar

bons (PFC), and (2) haemoglobin-based oxygen carriers (HBOCs), i.e., solutions based on isolated human or bovine haemoglobin.⁶¹

Perfluorocarbons (PFCs)

PFCs are simply constructed molecules (MW 450–500 D) derived from cyclic or straight-chain hydrocarbons with hydrogen atoms replaced by halogens (i.e. fluorine or bromide). PFCs are chemically and biologically inert; they are insoluble in water and therefore have to be emulsified for intravenous application. Oxygen kinetics of PFCs are characterized by a linear relationship between partial pressure of arterial oxygen and oxygen content; therefore high partial pressures of arterial oxygen are required to maximize the amount of oxygen transported by the PFC (Figure 3).⁶²

Oxygen release from PFC to the tissues is almost complete in the presence of a high pO_2 gradient between arterial blood and the tissues (cf. Figure 3). At a given pO_2 gradient of 560 mmHg (arterial blood 600 mmHg, tissue 40 mmHg), 100 g of a 60% (w/v) PFC emulsion (e.g. perfluorooctylbromide, Oxygent™, Alliance Corp., San Diego, CA, USA) release 15 mL oxygen.⁶³ The same amount of oxygen is provided by 450 mL of whole blood with a haemoglobin concentration of 14 g/dL. Additionally, PFCs enhance tissue oxygenation by lowering the diffusion barrier between erythrocytes and the plasma ('facilitated diffusion').⁶¹

After intravenous infusion, PFC emulsion droplets are rapidly taken up by the reticuloendothelial system (RES). To avoid RES overload and consequent immunosuppression, the clinical application of PFC is restricted to low dosages (e.g. maximum dose of 60% Oxygent™: 2.7 g/kg).

In elective surgery with anticipated substantial blood loss, a suitable application mode of PFC is represented by the concept of augmented haemodilution (A-ANH™, patented by Alliance Corp.): prior to surgery, autologous blood is harvested by ANH. During acellular fluid replacement of surgical blood loss, the combination of hyperoxic ventilation and repetitive co-administration of low boluses of PFC maintains adequate tissue oxygenation despite further decrease of haemoglobin concentration. In the best case, retransfusion of autologous blood can be postponed until bleeding is under control.^{64,65}

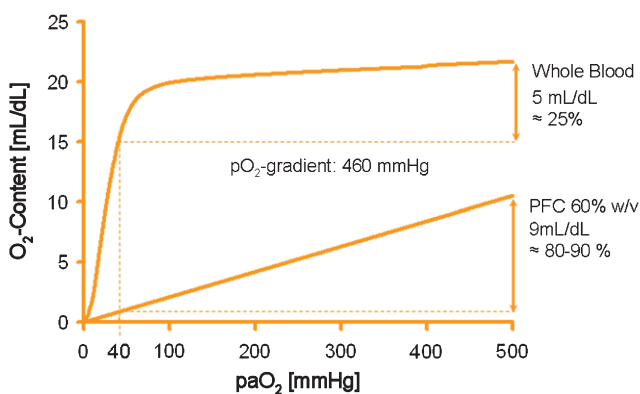


Figure 3. Oxygen dissociation kinetics of native blood (sigmoidal) and a 60% (w/v) Oxygent™ emulsion (linear). At a given tissue pO_2 of 40 mmHg, oxygen extraction from perfluorocarbon (PFC) is almost complete, in contrast to that from blood (oxygen extraction rate 80–90% PFC versus 25% blood).⁶³

In splenectomized dogs, this concept allowed the extension of acute normovolaemic anaemia from Hct 21% to Hct 8% without any signs of impaired tissue oxygenation or compromised myocardial contractility.^{25,66} In patients undergoing cardiac surgery, the application of 2.7 g/kg Oxygent™ provided adequate gastrointestinal tissue oxygenation at haemoglobin to 6.6 ± 0.4 g/dL.⁶⁷ In non-cardiac surgical patients (orthopaedic and general surgery), the low-dose-bolus administration of 60% Oxygent™ (0.9, 1.8 or 2.7 g/dL) allowed the transfusion of allogeneic blood to be postponed by 80 minutes.⁶⁸

In a recent multicentre phase-III study, the number of pRBC units transfused until postoperative day 3 was significantly lower in patients treated with PFC. However, aside from typical mild side-effects of PFC (flu-like symptoms, primarily fever, chills, headache, nausea and myalgia), an increased incidence of postoperative ileus has been reported.⁶⁹ Moreover, patient enrolment in a phase-III study in cardiac surgery was suspended in 2001 due to an increased rate of neurological complications.⁶² Nevertheless, the manufacturers are seeking to perform additional multicentre studies in Europe and the USA before filing for market approval.

Haemoglobin-based oxygen carriers (HBOC)

Haemoglobin used for manufacturing HBOCs originates from outdated human red cells or from bovine blood, or it is genetically engineered. Purified haemoglobin molecules are chemically modified to increase their stability and to modulate oxygen affinity. These chemical modifications include intramolecular cross-linking of α -subunits, polymerization of haemoglobin molecules using glutaraldehyde or o-raffinose, conjugation of polyethylene glycol to the surface of the haemoglobin molecule, insertion of 2,3-DPG analogues or embedding haemoglobin molecules into phospholipid vesicles (Table 5).⁷⁰

In contrast to PFCs, HBOCs feature sigmoidal oxygen kinetics. As indicated by high $p50$ values, the oxygen affinity of most HBOCs is lower than that in native human blood, facilitating the offloading of oxygen to the tissues.⁷¹ Moreover, extracellular haemoglobin possesses strong vasoconstrictive properties, the underlying mechanisms of which are: (1) scavenging of nitric oxide ('NO scavenging'); (2) augmented release of endothelin; and (3) stimulation of endothelin receptors and adrenoreceptors.⁷²

Due to their oncotic properties, most HBOCs can be characterized as 'oxygen-transporting plasma expanders' suitable for fluid resuscitation from haemorrhagic shock as well as for the treatment of surgical blood loss.

During fluid resuscitation from haemorrhagic shock, hypovolaemia can be treated effectively, while arterial oxygen content is maintained despite progressive dilutional anaemia. Indeed, in experimental studies of severe hemorrhagic shock, resuscitation with HBOCs consistently effected a sustained stabilization of the haemodynamics and tissue oxygenation and significantly decreased mortality.⁷³⁻⁷⁶ Moreover, the post-ischaemic interaction between leukocytes and the endothelium could be attenuated by infusion of HBOCs based on human^{77,78} as well as bovine haemoglobin.⁷⁹

Surprisingly, the long-time favourite among the HBOCs, DCLHb, was abandoned in 1998 after an interim analysis of a trauma study performed in the USA. After enrolment of 112 patients, the 24- and 48-hour mortality was significantly higher in patients treated with DCLHb.⁸⁰ Although severe deficiencies regarding design and performance of the study (under-resuscitation and over-proportional enrolment of

Table 5. Physicochemical characteristics and actual state of clinical research on haemoglobin-based oxygen carriers (HBOCs).

	Source of haemoglobin	Concentration (g/dL)	MW (Da)	P50 (mmHg)	Indication	Phase of clinical testing
PHP™	Human	8	123,000	23.6	Haemodynamic instability in septic shock	II/III
HemAssist™	Human	10	65,000	32	Reduction of perioperative transfusion rate	Up to III, stopped
r-Hb 1.1™	Recombinant	5–10	64,000	31–32	Reduction of perioperative transfusion rate	I/II, stopped
r-Hb 2.0™	Recombinant	10	320,000	31–32	Reduction of perioperative transfusion rate	I/II, stopped
Hemopure™	Bovine	13	250,000	38	Reduction of perioperative transfusion rate	III
Polyheme™	Human	10	150,000	26–32	Reduction of perioperative transfusion rate	III
Hemolink™	Human	10	120–180,000	39	Reduction of perioperative transfusion rate	III, discontinued
Hemospan™	Human	4	95,000	6	Reduction of perioperative transfusion rate	II

PHP™, pyridoxylated, polyethylene-glycol conjugated haemoglobin (Curacyte Health Sciences, Munich, Germany); HemAssist™, diaspirin cross-linked haemoglobin (DCLHb, Baxter Healthcare, Round Lake, USA); r-Hb 1.1, recombinant haemoglobin, version 1.1 (Somatogen Inc., Boulder, USA, later Baxter Healthcare); r-Hb 2.0, recombinant haemoglobin, version 2.0 (Baxter Healthcare); Hemopure™, polymerized bovine haemoglobin (HBOC 201, Biopure Corp., Cambridge, USA); Polyheme™, pyridoxylated, glutaraldehyde-polymerized haemoglobin (Northfiled Lab. Inc., Evanston, USA); Hemolink™, haemoglobin raffimer (Hemosol Inc., Toronto, Canada); Hemospan™, maleimide-activated polyethylene glycol-modified haemoglobin (MP4, Sangart INC, San Diego, USA).

desperate cases in the DCLHb group), the study has been terminated prematurely and has never been restarted.⁸¹

In contrast, PolyHeme™ proved to be an effective resuscitation fluid when 171 patients suffering massive haemorrhage were treated with this HBOC. Compared with a historical control group, 30-day mortality could be reduced significantly (64.5% versus 25%).⁸² However, this report does not comment on potential side-effects of PolyHeme™. Enrolment in another pre-hospital phase-III study has recently been completed, and the first results are not expected before autumn 2006.

Aside from fluid resuscitation from haemorrhagic shock, HBOCs are also suitable for the treatment of intraoperative blood loss. During isovolaemic replacement of lost blood, the oxygen-transport properties of the HBOC allow for haemodilution to a lower Hct than do crystalloid and colloid solutions. Hence, the transfusion of

allogeneic blood can be postponed until surgical bleeding is under control. HBOCs have been tested in several clinical phase-III studies, including cardiac and non-cardiac (general, vascular, trauma) surgery.^{82–90} Frequently observed side-effects consisted of increased systemic and pulmonary arterial resistances, decreased cardiac output, jaundice, and increased activities of amylase, lipase and hepatic transaminases.^{86–88,90} Whether the increased enzyme activities must be judged as signs of pancreatitis or whether they may be related to interference with photometric laboratory tests has to date not been fully elucidated.⁹¹

However, a sustained reduction of allogeneic blood transfusion (up to postoperative day 7) attributable to the use of an HBOC has been reported by only two authors^{83,88}, but the blood-sparing potential was limited to only 260–600 mL pRBC. The clinical relevance of this finding has been critically discussed by the authors themselves. A reason for the finding may be the short intravascular half-life of HBOCs. The short-term application only postpones the allogeneic blood transfusion. To achieve an effective reduction of RBC transfusions, HBOCs must be infused over a longer term, theoretically until the erythropoiesis can provide a sufficient quantity of autologous RBCs. Regarding the long-term use of HBOCs, only case reports are currently available.^{92,93}

Finally, the clinical impact of vasoconstrictive activity exerted by most HBOCs is not yet fully understood. Experimental data indicate that these properties may be harmful with respect to nutritional blood flow and organ function.^{94,95} Therefore the availability of a non-vasoactive HBOC may be desirable. Maleimide-activated polyethylene-glycol-modified haemoglobin (Hemospan™, Sangart Corp.) represents such an HBOC featuring a low haemoglobin concentration (4 g/dL), a high oxygen affinity (p50 5.9 mmHg) and a high viscosity (2.5 cP). These characteristics, at first sight counterintuitive, have been demonstrated to provide sufficient tissue oxygenation on the microcirculatory level.^{96,97} Currently, Hemospan™ has finished testing phases I and II, and a clinical phase-III trial is scheduled for 2006.⁹⁸

To date, no HBOC with worldwide approval is available for routine clinical use. Only the bovine HBOC Hemopure™ (Biopure Inc., Cambridge, USA) had been approved by the South African Ministry of Health in April 2001. The decisive factor for this regional approval might have been the high incidence of infectious diseases among blood donors in South Africa. However, in 2002, Biopure filed approval by the FDA, the procedure is still pending.⁷⁰ The blood-sparing potential of both types of artificial oxygen carrier currently under investigation (PFC and HBOCs) has been proven in experimental as well as in clinical studies. Nevertheless, the approval of a particular synthetic oxygen carrier by the FDA is not yet not foreseeable. Further research and development activities targeting the identification of an ideal oxygen carrier suitable for clinical use remains an issue of substantial interest.

Practice points

- the indication to transfuse allogeneic blood must be based on a critical judgement of necessity
- augmentation of anaemia tolerance allows a restrictive transfusion policy to be extended
- among autologous transfusion techniques, ANH and/or ICS are the most effective

Research agenda

- although the limits of total body anaemia tolerance are well known, further research is necessary to evaluate the specific anaemia tolerance of individual organs
- contraindications of ICS should be re-evaluated on the basis of systematic research
- research and development activities in the field of artificial oxygen carriers are still mandatory to prove the safety and efficacy of these 'blood substitutes'

REFERENCES

1. Goodnough LT. Risks of blood transfusion. *Critical Care Medicine* 2003; **31**: S678–S686.
2. Madjdpour C, Heindl V & Spahn DR. Risks, benefits, alternatives and indications of allogeneic blood transfusions. *Minerva Anestesiologica* 2006; **72**: 283–298.
3. Hebert PC, Wells GA, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *The New England Journal of Medicine* 1999; **340**: 409–417.
4. Vincent JL, Baron JF, Reinhart K et al. Anemia and blood transfusion in critically ill patients. *JAMA: The Journal of the American Medical Association* 2002; **288**: 1499–1507.
5. Corwin HL, Gettinger A, Pearl RG et al. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Critical Care Medicine* 2004; **32**: 39–52.
6. Taylor RW, O'Brien J, Trottier SJ et al. Red blood cell transfusions and nosocomial infections in critically ill patients. *Critical Care Medicine* 2006; **34**: 2302–2308.
7. Palmieri TL, Caruso DM, Foster KN et al. Effect of blood transfusion on outcome after major burn injury: a multicenter study. *Critical Care Medicine* 2006; **34**: 1602–1607.
8. Varney SJ & Guest JF. The annual cost of blood transfusions in the UK. *Transfusion Medicine (Oxford, England)* 2003; **13**: 205–218.
9. Goodnough LT, Shander A & Brecher ME. Transfusion medicine: looking to the future. *Lancet* 2003; **361**: 161–169.
10. Messmer KF. Acceptable hematocrit levels in surgical patients. *World Journal of Surgery* 1987; **11**: 41–46.
11. Spahn DR & Casutt M. Eliminating blood transfusions: new aspects and perspectives. *Anesthesiology* 2000; **93**: 242–255.
12. Habler OP & Messmer KF. The physiology of oxygen transport. *Transfusion Science* 1997; **18**: 425–435.
13. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *Journal of Applied Physiology* 1977; **42**: 228–234.
- *14. Meier JM, Kemming GI, Kisch-Wedel H et al. Hyperoxic ventilation reduces 6-hour mortality at the critical hemoglobin concentration. *Anesthesiology* 2004; **100**: 70–76.
15. Fontana JL, Welborn L, Mongan PD et al. Oxygen consumption and cardiovascular function in children during profound intraoperative normovolemic hemodilution. *Anesthesia and Analgesia* 1995; **80**: 219–225.
16. Zollinger A, Hager P, Singer T et al. Extreme hemodilution due to massive blood loss in tumor surgery. *Anesthesiology* 1997; **87**: 985–987.
17. van Citters RL & Franklin DL. Cardiovascular performance of Alaska sled dogs during exercise. *Circulation Research* 1969; **24**: 33–42.
- *18. Madjdpour C, Spahn DR & Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Critical Care Medicine* 2006; **34**: S102–S108.
19. Carson JL, Duff A, Poses RM et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1055–1060.
20. van der Linden P, De Hert S, Mathieu N et al. Tolerance to acute isovolemic hemodilution. Effect of anesthetic depth. *Anesthesiology* 2003; **99**: 97–104.

21. Vernon DD & Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. *Critical Care Medicine* 2000; **28**: 1569–1571.
22. Perez-de-Sa V, Roscher R, Cunha-Goncalves D et al. Mild hypothermia has minimal effects on the tolerance to severe progressive normovolemic anemia in Swine. *Anesthesiology* 2002; **97**: 1189–1197.
23. Habler OP & Messmer KF. Hyperoxaemia in extreme haemodilution. *British Journal of Anaesthesia* 1998; **81**(supplement 1): 79–82.
24. Pape A, Meier J, Kertscho H et al. Hyperoxic ventilation increases the tolerance of acute normovolemic anemia in anesthetized pigs. *Critical Care Medicine* 2006; **34**: 1475–1482.
25. Habler OP, Kleen MS, Hutter JW et al. Hemodilution and intravenous perflubron emulsion as an alternative to blood transfusion: effects on tissue oxygenation during profound hemodilution in anesthetized dogs. *Transfusion* 1998; **38**: 145–155.
26. Habler OP, Kleen MS, Hutter JW et al. Effects of hyperoxic ventilation on hemodilution-induced changes in anesthetized dogs. *Transfusion* 1998; **38**: 135–144.
27. Habler O. Cardiac high-risk patients: From 'permissive' to 'deliberate' anemia. *Critical Care Medicine* 2005; **33**: 2434–2435.
28. Vamvakas EC & Pineda AA. Autologous transfusion and other approaches to reduce allogeneic blood exposure. *Baillière's Best Practice & Research. Clinical Haematology* 2000; **13**: 533–547.
29. Karger R & Kretschmer V. Modern concepts of autologous haemotherapy. *Transfusion and Apheresis Science* 2005; **32**: 185–196.
30. Rogers BA & Johnstone DJ. Audit on the efficient use of cross-matched blood in elective total hip and total knee replacement. *Annals of the Royal College of Surgeons of England* 2006; **88**: 199–201.
31. Hutton B, Fergusson D, Tinmouth A et al. Transfusion rates vary significantly amongst Canadian medical centres. *Canadian Journal of Anaesthesia* 2005; **52**: 581–590.
32. Keating EM & Meding JB. Perioperative blood management practices in elective orthopaedic surgery. *The Journal of the American Academy of Orthopaedic Surgeons* 2002; **10**: 393–400.
33. Habler OP & Messmer KF. Verfahren zur Reduktion von Fremdblut in der operativen Medizin. *Anaesthesist* 1997; **46**: 915–926.
- *34. Shander A. Surgery without blood. *Critical Care Medicine* 2003; **31**: S708–S714.
- *35. Carless P, Moxey A, O'Connell D & Henry D. Autologous transfusion techniques: a systematic review of their efficacy. *Transfusion Medicine (Oxford, England)* 2004; **14**: 123–144.
- *36. Messmer K & Sunder-Plassmann L. Hemodilution. *Progress in Surgery* 1974; **13**: 208–245.
37. Murray D. Acute normovolemic hemodilution. *European Spine Journal* 2004; **13**: S72–S75.
38. Weiskopf RB. Efficacy of acute normovolemic hemodilution assessed as a function of fraction of blood volume lost. *Anesthesiology* 2001; **94**: 439–446.
- *39. Matot I, Scheinin O, Jurim O & Eid A. Effectiveness of acute normovolemic hemodilution to minimize allogeneic blood transfusion in major liver resections. *Anesthesiology* 2002; **97**: 794–800.
40. Wong JC, Torella F, Haynes SL et al. Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial. *Annals of Surgery* 2002; **235**: 145–151.
41. Bennett J, Haynes S, Torella F et al. Acute normovolemic hemodilution in moderate blood loss surgery: a randomized controlled trial. *Transfusion* 2006; **46**: 1097–1103.
42. Terada N, Arai Y, Matsuta Y et al. Acute normovolemic hemodilution for radical prostatectomy: can it replace preoperative autologous blood transfusion? *International Journal of Urology* 2001; **8**: 149–152.
43. Habler OP, Schwenzler K, Zimmer K et al. Effects of standardized acute normovolemic hemodilution on intraoperative allogeneic blood transfusion in patients undergoing major maxillofacial surgery. *International Journal of Oral and Maxillofacial Surgery* 2004; **33**: 467–475.
44. Bryson GL, Laupacis A & Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. The International Study of Perioperative Transfusion. *Anesthesia and Analgesia* 1998; **86**: 9–15.
45. Segal JB, Blasco-Colmenares E, Norris EJ & Guallar E. Preoperative acute normovolemic hemodilution: a meta-analysis. *Transfusion* 2004; **44**: 632–644.
46. Monk TG, Goodnough LT, Brecher ME et al. A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. *Anesthesiology* 1999; **91**: 24–33.
47. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; **105**: 198–208.

48. Cuenca J, Garcia-Erce JA, Martinez F et al. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. *Transfusion* 2006; **46**: 1112–1119.
49. Andrews CM, Lane DW & Bradley JG. Iron pre-load for major joint replacement. *Transfusion Medicine (Oxford, England)* 1997; **7**: 281–286.
50. Goodnough LT, Skikne B & Brugnara C. Erythropoietin, iron, and erythropoiesis. *Blood* 2000; **96**: 823–833.
51. Chun TY, Martin S & Lepor H. Preoperative recombinant human erythropoietin injection versus preoperative autologous blood donation in patients undergoing radical retropubic prostatectomy. *Urology* 1997; **50**: 727–732.
52. Dai B, Wang L, Djaiani G & Mazer CD. Continuous and discontinuous cell-washing autotransfusion systems. *Journal of Cardiothoracic and Vascular Anesthesia* 2004; **18**: 210–217.
53. Waters JH. Indications and contraindications of cell salvage. *Transfusion* 2004; **44**: 40S–44S.
54. Bowley DM, Barker P & Boffard KD. Intraoperative Blood Salvage in Penetrating Abdominal Trauma: a Randomised, Controlled Trial. *World Journal of Surgery* 2006; **30**: 1074–1080.
55. Hansen E, Bechmann V & Altmeyen J. Intraoperative blood salvage in cancer surgery: safe and effective? *Transfusion and Apheresis Science* 2002; **27**: 153–157.
56. Beck-Schimmer B, Romero B, Booy C et al. Release of inflammatory mediators in irradiated cell salvage blood and their biological consequences in human beings following transfusion. *European Journal of Anaesthesiology* 2004; **21**: 46–52.
57. Catling S & Joels L. Cell salvage in obstetrics: the time has come. *BJOG: an International Journal of Obstetrics and Gynaecology* 2005; **112**: 131–132.
58. Waters JH, Biscotti C, Potter PS & Phillipson E. Amniotic fluid removal during cell salvage in the cesarean section patient. *Anesthesiology* 2000; **92**: 1531–1536.
- *59. Huet C, Salmi LR, Fergusson D et al. A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. International Study of Perioperative Transfusion (ISPO-T) Investigators. *Anesthesia and Analgesia* 1999; **89**: 861–869.
60. Gohel MS, Bulbulia RA, Slim FJ et al. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). *Annals of the Royal College of Surgeons of England* 2005; **87**: 3–14.
- *61. Habler OP, Pape A, Meier J & Zwissler B. Künstliche Sauerstoffträger als Alternative zur Bluttransfusion. *Anaesthesist* 2005; **54**: 741–754.
- *62. Spahn DR & Kocian R. Artificial O₂ carriers: status in 2005. *Current Pharmaceutical Design* 2005; **11**: 4099–4114.
63. Riess JG. Understanding the fundamentals of perfluorocarbons and perfluorocarbon emulsions relevant to in vivo oxygen delivery. *Artificial Cells, Blood Substitutes, and Immobilization Biotechnology* 2005; **33**: 47–63.
64. Spahn DR, Willmann PF & Faithfull NS. Die Wirksamkeit der Augmentierten Akuten Normovolämischen Hämodilution (A-ANH™). *Anaesthesist* 2001; **50**(supplement 1): S49–S54.
65. Spahn DR & Kocian R. The place of artificial oxygen carriers in reducing allogeneic blood transfusions and augmenting tissue oxygenation. *Canadian Journal of Anaesthesia* 2003; **50**: S41–S47.
66. Habler OP, Kleen MS, Hutter JW et al. IV perflubron emulsion versus autologous transfusion in severe normovolemic anemia: effects on left ventricular perfusion and function. *Research in Experimental Medicine* 1998; **197**: 301–318.
67. Frumento RJ, Mongero L, Naka Y & Benett-Guerrero E. Preserved gastric tonometric variables in cardiac surgical patients administered intravenous perflubron emulsion. *Anesthesia and Analgesia* 2002; **94**: 809–814.
68. Spahn DR, van BR, Theilmeier G et al. Perflubron emulsion delays blood transfusions in orthopedic surgery. European Perflubron Emulsion Study Group. *Anesthesiology* 1999; **91**: 1195–1208.
69. Spahn DR, Waschke KF, Standl T et al. Use of perflubron emulsion to decrease allogeneic blood transfusion in high-blood-loss non-cardiac surgery: results of a European phase 3 study. *Anesthesiology* 2002; **97**: 1338–1349.
70. Pape A, Kertscho H, Meier J et al. Overview of artificial O₂ carriers. *ISBT Science Series* 2006; **1**(1): 152–160.
71. Moore EE. Blood substitutes: the future is now. *Journal of the American College of Surgeons* 2003; **196**: 1–17.

72. Alayash AI. Hemoglobin-based blood substitutes: oxygen carriers, pressor agents, or oxidants? *Nature Biotechnology* 1999; **17**: 545–549.
73. Habler OP, Kleen MS, Pape A et al. Diaspirin-crosslinked hemoglobin reduces mortality of severe hemorrhagic shock in pigs with critical coronary stenosis. *Critical Care Medicine* 2000; **28**: 1889–1898.
74. Nolte D, Steinhäuser P, Pickelmann S et al. Effects of diaspirin-cross-linked hemoglobin (DCLHb) on local tissue oxygen tension in striated skin muscle: an efficacy study in the hamster. *The Journal of Laboratory and Clinical Medicine* 1997; **130**: 328–338.
75. Schultz SC, Hamilton INJ & Malcolm DS. Use of base deficit to compare resuscitation with lactated Ringer's solution, Haemaccel, whole blood, and diaspirin cross-linked hemoglobin following hemorrhage in rats. *The Journal of Trauma* 1993; **35**: 619–625.
76. Sprung J, Mackenzie CF, Barnas GM et al. Oxygen transport and cardiovascular effects of resuscitation from severe hemorrhagic shock using hemoglobin solutions. *Critical Care Medicine* 1995; **23**: 1540–1553.
77. Johnson JL, Moore EE, Gonzalez RJ et al. Alteration of the postinjury hyperinflammatory response by means of resuscitation with a red cell substitute. *The Journal of Trauma* 2003; **54**: 133–139.
78. Pickelmann S, Nolte D, Leiderer R et al. Attenuation of posts ischemic reperfusion injury in striated skin muscle by diaspirin-cross-linked Hb. *The American Journal of Physiology* 1998; **275**: H361–H368.
79. Botzlar A, Nolte D & Messmer K. Effects of ultra-purified polymerized bovine hemoglobin on the microcirculation of striated skin muscle in the hamster. *European Journal of Medical Research* 1996; **1**: 471–478.
80. Sloan EP, Koenigsberg M, Gens D et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. *JAMA: The Journal of the American Medical Association* 1999; **282**: 1857–1864.
81. Sloan EP, Koenigsberg M, Brunett PH et al. Post hoc mortality analysis of the efficacy trial of diaspirin cross-linked hemoglobin in the treatment of severe traumatic hemorrhagic shock. *The Journal of Trauma* 2002; **52**: 887–895.
82. Gould SA, Moore EE, Hoyt DB et al. The life-sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. *Journal of the American College of Surgeons* 2002; **195**: 445–452.
83. Cheng DC, Mazer CD, Martineau R et al. A phase II dose-response study of hemoglobin raffimer (Hemolink) in elective coronary artery bypass surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2004; **127**: 79–86.
84. Greenburg AG & Kim HW. Use of an oxygen therapeutic as an adjunct to intraoperative autologous donation to reduce transfusion requirements in patients undergoing coronary artery bypass graft surgery. *Journal of the American College of Surgeons* 2004; **198**: 373–383.
85. Garrioch MA, McClure JH & Wildsmith JA. Haemodynamic effects of diaspirin crosslinked haemoglobin (DCLHb) given before abdominal aortic aneurysm surgery. *British Journal of Anaesthesia* 1999; **83**: 702–707.
86. Kasper SM, Walter M, Grune F et al. Effects of a hemoglobin-based oxygen carrier (HBOC-201) on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. *Anesthesia and Analgesia* 1996; **83**: 921–927.
87. Lamy ML, Daily EK, Brichtant JF et al. Randomized trial of diaspirin cross-linked hemoglobin solution as an alternative to blood transfusion after cardiac surgery. The DCLHb Cardiac Surgery Trial Collaborative Group. *Anesthesiology* 2000; **92**: 646–656.
88. Schubert A, Przybelski RJ, Eidt JF et al. Diaspirin-crosslinked hemoglobin reduces blood transfusion in noncardiac surgery: a multicenter, randomized, controlled, double-blinded trial. *Anesthesia and Analgesia* 2003; **97**: 323–332.
89. Hayes JK, Stanley TH, Lind GH et al. A double-blind study to evaluate the safety of recombinant human hemoglobin in surgical patients during general anesthesia. *Journal of Cardiothoracic and Vascular Anesthesia* 2001; **15**: 593–602.
90. Sprung J, Kindscher JD, Wahr JA et al. The use of bovine hemoglobin glutamer-250 (Hemopure) in surgical patients: results of a multicenter, randomized, single-blinded trial. *Anesthesia and Analgesia* 2002; **94**: 799–808.
91. Kazmierczak SC, Catrou PG, Best AE et al. Multiple regression analysis of interference effects from a hemoglobin-based oxygen carrier solution. *Clinical Chemistry and Laboratory Medicine* 1999; **37**: 453–464.

92. Mullon J, Giacompe G, Clagett C et al. Transfusions of polymerized bovine hemoglobin in a patient with severe autoimmune hemolytic anemia. *The New England Journal of Medicine* 2000; **342**: 1638–1643.
93. Lanzkron S, Moliterno AR, Norris EJ et al. Polymerized human Hb use in acute chest syndrome: a case report. *Transfusion* 2002; **42**: 1422–1427.
94. Pape A, Kleen MS, Kemming GI et al. Fluid resuscitation from severe hemorrhagic shock using dapsirin cross-linked hemoglobin fails to improve pancreatic and renal perfusion. *Acta Anaesthesiologica Scandinavica* 2004; **48**: 1328–1337.
95. Pape A, Kemming GI, Meisner FG et al. Dapsirin cross-linked hemoglobin fails to improve left ventricular diastolic function after fluid resuscitation from hemorrhagic shock. *European Surgical Research* 2001; **33**: 318–326.
96. Vandegriff KD, Malavalli A, Wooldridge J et al. MP4, a new nonvasoactive PEG-Hb conjugate. *Transfusion* 2003; **43**: 509–516.
97. Wettstein R, Tsai AG, Erni D et al. Resuscitation with polyethylene glycol-modified human hemoglobin improves microcirculatory blood flow and tissue oxygenation after hemorrhagic shock in awake hamsters. *Critical Care Medicine* 2003; **31**: 1824–1830.
- *98. Winslow RM. Current status of oxygen carriers ('blood substitutes'): 2006. *Vox Sanguinis* 2006; **91**: 102–110.
99. van Woerkens EC, Trouwborst A & van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesthesia and Analgesia* 1992; **75**: 818–821.
100. Kemming GI, Meisner FG, Kleen MS et al. Hyperoxic ventilation at the critical haematocrit. *Resuscitation* 2003; **56**: 289–297.
101. Meisner FG, Kemming GI, Habler OP et al. Dapsirin crosslinked hemoglobin enables extreme hemodilution beyond the critical hematocrit. *Critical Care Medicine* 2001; **29**: 829–838.



ELSEVIER

Best Practice & Research Clinical Anaesthesiology
Vol. 21, No. 2, pp. 241–256, 2007
doi:10.1016/j.bpa.2007.02.002
available online at <http://www.sciencedirect.com>



7

Perioperative use of anti-platelet drugs

Pierre-Guy Chassot* PD, MER

Staff member

Department of Anaesthesiology, University Hospital Lausanne (CHUV),
Bugnon 46, CH - 1011 Lausanne, Switzerland

Alain Delabays

Consultant Cardiologist

Department of Cardiology, University Hospital Lausanne (CHUV), CH - 1011 Lausanne, Switzerland

Donat R. Spahn FRCA

Chairman of the Department

Department of Anaesthesiology, University Hospital Zürich (USZ), CH - 8091 Zürich, Switzerland

Performing a surgical procedure on a patient undergoing anti-platelet therapy raises a dilemma: is it safer to withdraw the drugs and reduce the haemorrhagic risk, or to maintain them and reduce the risk of myocardial ischaemic events? Based on recent clinical data, this review concludes that the risk of coronary thrombosis on anti-platelet drugs withdrawal is much higher than the risk of surgical bleeding when maintaining them. In secondary prevention, aspirin is a lifelong therapy and should never be stopped. Clopidogrel is mandatory as long as the coronary stents are not fully endothelialized, which takes 6–24 weeks depending on the technique used, but might be required for a longer period.

Key words: anti-platelet therapy; non-cardiac surgery; coronary stent thrombosis; surgical haemorrhage.

With the increasing prevalence of coronary artery disease (CAD) and the progressive aging of the population, it can be estimated that there are two million candidates for coronary dilatation in Western Europe and the US each year.¹ Currently, over 90% of all percutaneous coronary interventions (PCIs) involve the placement of stents. Recent data suggest that 5% of patients who underwent PCI will also undergo non-cardiac

* Corresponding author. Tel.: +41 21 314 2061; Fax: +41 21 314 2004.
E-mail address: pierre-guy.chassot@chuv.ch (P.-G. Chassot).

surgery within the first year after coronary stenting.² The high success rate obtained with the new coronary stents is linked, at least partially, to the prolonged intake of anti-platelet (AP) medication. Moreover, situations other than coronary stenting require the protection of AP drugs and increase the probability of meeting patients under AP therapy: previous myocardial infarction (MI), cerebrovascular disease, peripheral vasculopathy, or primary prevention in case of multiple cardiovascular risk factors.

Therefore, anaesthesiologists are more and more frequently confronted with a new situation: how to manage a patient on aspirin and clopidogrel after a recent PCI who is to undergo a potentially haemorrhagic surgical procedure? They are faced with a dilemma: stopping the drugs increases the risk of stent thrombosis, but maintaining them increases the risk of haemorrhage. The usual attitude is to withdraw all AP drugs 1 week prior to surgery, but recent data suggest that this might be extremely dangerous for the patients. It is therefore of the utmost importance to adjust the current practice concerning the use of AP drugs in the perioperative period.

THE VULNERABLE PATIENT

The purpose of AP therapy is to decrease the patient's vulnerability towards cardiovascular and cerebrovascular accidents. Vulnerable cardiovascular patients are those susceptible to having a serious cardiovascular event in the future, which includes acute coronary syndrome or sudden cardiac death. Their probability is based on three elements: the instability of atheromatous plaques, the susceptibility of the myocardium, and the thrombogenicity of the blood.³

Unstable atheromatous plaques

Three quarters of sudden cardiac events (acute coronary syndrome and/or sudden cardiac death) are due to atheromatous plaque rupture.⁴ These plaques are characterized by a large lipid core covered by a thin cap; they are densely infiltrated by macrophages, with signs of active inflammation. Multiple humoral and neuro-vegetative triggers may destabilize the atheromatous plaque and lead to the development of an occluding thrombus. Although the following classification is very much simplified, postoperative MI can be divided in two different categories of approximately equal incidence⁵⁻⁷:

1. Infarction appearing in myocardial areas supplied by coronary arteries with tight stenosis. The triggering factor is a mismatch between an increased oxygen demand (tachycardia, hypertension, pain, stress) and a poor oxygen supply (coronary stenosis, tachycardia, hypovolaemia, anaemia) (*demand ischaemia*). Usually, this non-Q MI follows a period of ST-segment depression (subendocardial infarction); its peak incidence is at the third or fourth postoperative day, and its most effective prevention is β -blockade.
2. Infarction due to disruption and thrombosis of an unstable plaque. This MI appears in myocardial areas supplied by moderate coronary stenosis on angiogram (<60%)⁸ which are usually silent on stress test (*supply ischaemia*).⁹ It is characterized by an elevation of the ST-segment and a Q wave (transmural infarction); it appears earlier (<36 postoperative hours), and its most effective prevention is anti-platelet drugs (aspirin and clopidogrel) and probably statins.

Myocardial susceptibility

The myocardium modulates the effects of acute coronary ischaemia depending on its degree of sympathetic stimulation, its susceptibility to ventricular arrhythmias, and its previous damage due to chronic ischaemia or cardiomyopathy.³ Intra- and postoperative periods are very complex situations because of a blending of harmful effects (sympathetic stimulation, haemorrhage) and beneficial effects (continuous monitoring, weakening of stress reaction by deep anaesthesia, preconditioning effect of halogenated agents).

Blood coagulability and acute-phase reaction

A number of serological markers may predict a patient's risk of cardiovascular complications: high low-density lipoprotein (LDL), low high-density lipoprotein (HDL), circulating non-esterified fatty acids, interleukin-6, and C-reactive protein (CRP).¹⁰ Several blood abnormalities such as anti-thrombin III and protein S deficiencies, and genetic polymorphisms such as GP IIb/IIIa receptor polymorphism, are related to blood vulnerability to thrombosis.¹¹ Acute coronary syndromes are linked with proinflammatory and prothrombotic conditions that involve an increased level of fibrinogen, CRP and plasminogen activator inhibitor.¹² The importance of the equilibrium between procoagulatory and fibrinolytic systems is demonstrated by several autopsy findings of old plaque disruption without vessel occlusion or myocardial infarction.¹³ In the perioperative setting, this harmonious balance is disrupted in favour of vessel thrombosis. Surgery is a high-risk situation because of the increased release of endogenous catecholamines in the postoperative period, much higher than in known triggers such as intense exercise or cigarette smoking.¹⁴ The postoperative risk of acute coronary syndrome is aggravated by the increased platelet adhesiveness and decreased fibrinolysis which are characteristic of the acute-phase reaction.¹⁵ It is therefore understandable that AP drugs are particularly helpful when the thrombogenic risk is highest.

USEFULNESS OF ANTI-PLATELET DRUGS

AP drugs are indicated for primary and secondary prevention of heart and brain vascular accidents. There are three different types of AP drugs:

- Acetylsalicylic acid (ASA, aspirin). The usual dosage is 50–300 mg/day; this is adapted to body weight, but, for a normal adult, a daily dose beyond 150 mg increases hemorrhagic risk without offering more protection.¹⁶ In primary protection, ASA is indicated when the 10-year risk of vascular accidents is more than 10%.¹⁷ In secondary prevention, ASA decreases myocardial reinfarction rate by 30% and subsequent stroke by 25%.^{18,19} ASA is a lifelong therapy which should never be discontinued after a coronary or cerebrovascular event.^{20–22}
- Clopidogrel (Plavix[®]; loading dose: 300 mg, daily dose: 75 mg) decreases the risk of MI in unstable angina by 18% and the risk of coronary stent thrombosis and recurrent stroke by 30%.^{1,23,24} The half-life of clopidogrel is short (4 hours), but recovery from the drug is long because of irreversible platelet inhibition; normal coagulation relies on the formation of new platelets, but not on the disappearance of the substance from the plasma. Therefore, clopidogrel is stopped for at least 7 days

preoperatively.²⁵ In emergency situations, haemostasis can be restored by administration of fresh platelets within a few hours of the last clopidogrel intake.

- Platelet glycoprotein IIb/IIIa receptor antagonists are used for the prevention of immediate thrombosis of coronary stents and are prescribed for 24–48 hours after PCI.²⁶ Abciximab (ReoPro[®]) has a half-life of 23 hours, whereas tirofiban (Aggrastat[®]) and eptifibatide (Integrilin[®]) have a half-life of 2 hours.²⁷ In case of surgery within 48 hours after abciximab, platelet transfusions are mandatory; beyond 6 hours after tirofiban or eptifibatide, platelet function returns to 90% of normal and bleeding time is prolonged <1.5 times.²⁸
- A bi-therapy (ASA + clopidogrel) is required in cases of unstable plaque and during the re-endothelialization phase of coronary stents. Clopidogrel can be substituted for ASA in non-responders or in case of allergic reactions.

A substantial proportion of patients does not respond to ASA (12–20%), particularly women and diabetics, and to clopidogrel (6–24%).²⁹ The wide variation in prevalence is due to the multiplicity of tests used to quantify ASA effects and to the absence of an effective test for evaluating clopidogrel efficiency.³⁰ The resistance to AP drugs might explain the high incidence of MI recurrence or stent thrombosis in some patients. Studies tend to show that patients with previous stent thrombosis have an impaired response to ASA, which may be overcome by additional treatment with clopidogrel.³¹ Specific gene variants implicated in thrombosis might have an impact on the efficiency of AP strategies. For example, the effect of ASA on platelet function is modified by the glycoprotein IIIa nucleotide polymorphism P1^{A2}; patients who are heterozygous for this gene keep a high platelet adhesiveness under ASA therapy, whereas adhesiveness is efficiently blunted in homozygotes at the same dosage.¹¹ In the near future, pharmacogenomics might be able to set up tests differentiating responders from non-responders; it will then be possible to tailor AP therapy to the patient's profile and improve the success rate of coronary revascularization.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

Coronary revascularization is the first-choice therapy for severe coronary artery disease or unstable coronary syndromes. A successful revascularization places the patient in a low-risk category, as if the coronary disease were cured, as long as he/she is asymptomatic without treatment other than ASA. However, the period immediately after any intra-coronary instrumentation is a high-risk period because the previously stenotic lesion is momentarily transformed into an unstable area since its endothelial covering is ruptured. After simple dilatation, it takes 2–4 weeks for the endothelium to be completely healed. A bare metallic stent (BMS) is first covered by a thin layer of smooth muscular cells in approximately 6 weeks; 6 more weeks are necessary for a complete endothelial covering.^{32,33} The duration of re-endothelialization determines the duration of clopidogrel treatment, which is mandatory as long as the prosthetic material is not fully covered. The minimal duration is variable, depending on the type of procedure (Table 1).^{20,22,34,35}

With a full anti-platelet coverage, the 30-day stent thrombosis rate is less than 1%, but the bare metal stents are threatened by an overgrowth of endothelium, which leads to a restenosis rate of 12–30% at 6–12 months.²² In order to counteract this phenomenon, the new 'drug-eluting' stents (DES) are covered with a fine layer of anti-proliferative agents, namely sirolimus or paclitaxel. With this technique, the

Table 1. Duration of anti-platelet therapy after percutaneous coronary intervention (PCI).

- Dilatation without stenting: 2–4 weeks
- Bare metal stent: 4–6 weeks
- Drug-eluting stent (sirolimus; Cypher™): 3 months
- Drug-eluting stent (paclitaxel; Taxus™, Achieve™, V-flex): 6 months
- Brachytherapy: 12 months
- Safety precaution after drug-eluting stent: clopidogrel up to 12 months
- Aspirin: lifelong therapy

restenosis rate has dropped to 0.5–1.5% at 1 year.^{36,37} The drawback is a delayed complete re-endothelialization and a prolonged AP therapy with ASA and clopidogrel: at least 3 months for sirolimus and 6 months for paclitaxel.

The PCI Cure study, which consisted of 2658 patients with acute coronary syndrome undergoing PCI randomly assigned to 1-year treatment with clopidogrel or placebo, disclosed an overall reduction of 31% ($P = 0.002$) in cardiovascular mortality or myocardial infarction rate in the clopidogrel group.²⁴ The difference between the two groups appears during the first 3 months, and stays constant thereafter. This raises the question of the usefulness of clopidogrel beyond 1 year. The CHARISMA study tried to answer this point³⁸: 15,603 high-risk cardiovascular patients were randomly assigned to receive clopidogrel or placebo and low-dose ASA, and were followed for a median of 28 months. The similar rates of MI, stroke or cardiovascular death in both groups revealed that clopidogrel plus aspirin was not more effective than aspirin alone for primary prevention. Moreover, the rate of severe spontaneous bleeding was increased (2.1% versus 1.3%). In secondary prevention, a small (12%) reduction in relative risk was observed in the clopidogrel group, but also with a slight increase in the bleeding risk. Therefore there are no hard data to support the use of clopidogrel beyond 1 year after PCI or cardiovascular event, except in some particularly unstable cases. On the other hand, ASA is a lifelong therapy and should never be interrupted whatever types of stents are used.

DELAYS AFTER CORONARY REVASCULARIZATION

As already mentioned, the weeks following a PCI are particularly dangerous because the coronary vessel is not yet covered by an endothelial layer. When patients undergo non-cardiac surgery during this period, their MI and mortality rates (average 30% and 20–40% respectively) are 5–10 times higher than the rates of matched patients undergoing the same operations under maximal medical therapy or after appropriate delays.^{2,39–41} The closer the PCI is to the operation, the higher the operative risk: mortality is 26% and non-fatal MI rate is 35% within 3 weeks⁴¹, but decrease to 5% after 2–3 months and to $\leq 1\%$ beyond 3 months.^{39–42} The same pattern appears after surgical revascularization (coronary artery bypass graft, CABG): mortality rate is 20.6% within 4 weeks after CABG and 3.9% at 2 months.⁴³ Major vascular surgery is particularly dangerous, and abdominal aneurysm resection during the first month post-CABG has a mortality rate of 28%.

We lack high-level-of-evidence studies on the optimal delays between revascularization and non-cardiac surgery. Therefore, the usual recommendations are based rather on the principles of safety and precaution^{20,34}:

- after CABG: 6 weeks;
- after PCI with simple dilatation (no stenting): 2–4 weeks;
- after PCI with bare metal stents: 6–8 weeks;
- after PCI with drug-eluting stents: 3 months (sirolimus) or 6 months (paclitaxel).

All patients are kept under ASA therapy in the perioperative period. When clopidogrel is indicated by the coronary status (Table 1), it is continued throughout the operation without interruption.

The studies comparing preoperatively revascularized CAD patients to non-revascularized patients with full medical treatment (β -blockers, statins, AP drugs) have not disclosed any significant difference in the rate of postoperative ischaemic complications between the two groups.^{44,45} Revascularization is based on coronary angiogram results, but half of the postoperative MI cases are linked to the thrombosis of an unstable plaque and occur in myocardial areas that are dependent on arteries with a non-significant stenosis.^{5,8} Moreover, coronary revascularization and non-cardiac operations are added risks and have cumulative mortality rates. For vascular patients, for example, the sum of the mortalities of revascularization and non-cardiac surgery is clearly higher than the mortality of non-cardiac surgery without revascularization but under optimal pharmacological protection with β -blockers, statin and aspirin.^{46,47} Therefore, preoperative coronary revascularization may be indicated only if some prerequisites are fulfilled:

- the indication is based on the coronary status, and is the same as outside the surgical context;
- the safety delays between revascularization and non-cardiac surgery (6–24 weeks, depending on the technique used) must be compatible with the clinical evolution of the surgical disease; this might not be the case for malignant tumours, aneurysms, incapacitating bone fractures, bowel obstruction, etc;
- the added risks of revascularization and non-cardiac surgery must be less than the risk of surgery under medical protection; this happens only in the case of very unstable CAD and expected delays between PCI/CABG and non-cardiac operation.

WITHDRAWAL OF ANTI-PLATELET DRUGS

It is a generally accepted policy to withdraw AP medications 7–10 days prior to a surgical or endoscopic procedure in order to prevent excessive bleeding. Knowing the efficiency of these drugs in preventing coronary stent thrombosis or MI and stroke recurrences, this attitude raises two important questions: how safe is it to abruptly interrupt AP therapy, and is bleeding really a major problem under continuous AP treatment?

Acute withdrawal of AP agents induces a deleterious rebound effect; prothrombotic phenomena overrule the physiological balance. An excessive thromboxane A_2 activity and a decreased fibrinolysis have been noticed on aspirin interruption.^{48,49} In a study of 2229 patients with DES and a thrombosis rate of 1.5% during the first year, premature discontinuation of AP therapy is the most significant independent predictor of stent thrombosis, with a hazard ratio of 57.13 ($P < 0.001$) and a mortality rate linked to stent thrombosis of 45%.³⁶ Another study shows that two thirds of the late DES thromboses are linked to AP withdrawal.³⁷ Compared to patients who have taken AP drugs without interruption, patients who stopped clopidogrel during the first month after PCI are ten times more likely to die (7.5% versus 0.7%, $P < 0.0001$) or to be rehospitalized (23% versus 14%, $P = 0.08$) during the next 11

months.⁵⁰ Stopping ASA, even as long as 15 months after PCI, may precipitate DES thrombosis and acute MI.^{51,52} The risk of non-fatal MI or cardiac death following acute coronary syndrome is twice as high in patients who have interrupted their AP drugs within 3 weeks (21.9% and 19.2% respectively) compared to those who are still under therapy (12.4% and 9.9% respectively).⁵³

These studies have been conducted outside surgery, but the situation is even worse in the postoperative period: the withdrawal of AP treatment to allow non-cardiac surgery within 3 weeks after PCI and stenting has resulted in mortalities between 30%⁵⁴ and 85%.⁴¹ The acute stent thrombosis has such a dramatic death rate because it corresponds to the abrupt interruption of flow in a coronary vessel where the output had been maintained; the involved myocardial territory is neither collateralized nor pre-conditioned by recurrent chronic ischaemic episodes.

HAEMORRHAGIC RISK

If the thrombotic risk at AP withdrawal is so high, what is the real danger of surgery under continuous AP therapy? In large cardiological studies, the rate of severe spontaneous bleeding is increased in patients under bi-therapy compared to those on ASA alone; it increased from 0.7% to 1.13% (37% increase in relative risk) in the ATC trial¹⁸, or from 2.7% to 3.7% (27% increase in relative risk) in the CURE trial.²³ The studies on intraoperative haemorrhagic risk of AP therapy are numerous but usually statistically underpowered. Large prospective randomized studies are rare, most reports being retrospective or anecdotal. The investigations have been carried out mainly in orthopaedics (hip arthroplasty) and in cardiac surgery (CABG). Nevertheless, the analysis of this literature reveals interesting facts concerning the impact of aspirin and clopidogrel on surgical bleeding.

Patients on ASA

A large review and meta-analysis of 474 studies devoted to the impact of aspirin prophylaxis on surgical blood loss has disclosed that patients on ASA alone have an intraoperative haemorrhagic risk increased by an average factor of 1.5 without an increase in surgical mortality or morbidity.⁵⁵ Despite a modest rise in bleeding rate, there are no modifications in surgical complications linked to haemorrhage in dental surgery, ophthalmology, visceral surgery, endoscopies and biopsies. In vascular surgery, the increase in bleeding complications is only 2.46%.²¹ In orthopaedics, the data are controversial: studies have shown an increased rate of bleeding and transfusion in hip arthroplasty⁵⁶ but not in femoral neck fracture osteosynthesis⁵⁷ or spinal instrumentation and multilevel fusion surgery.⁵⁸ Although aspirin increases bleeding by approximately 50%, surgeons unaware of aspirin application could not always differentiate patients on aspirin from patients off aspirin just from surgical bleeding.⁵⁹

Aspirin seems to be associated with a rise in bleeding rate only in specific procedures. After tonsillectomy, the reoperation rate for postoperative haemorrhage is increased 7.2 times in the aspirin group compared to the paracetamol group.⁶⁰ During transurethral prostatectomy, blood transfusion rate is increased by a factor of 2.7 in patients on aspirin compared to control groups⁵⁵; more importantly, there are two reported cases of fatalities in patients on low-dose aspirin.⁶¹ The new laser technique for endoscopic prostatectomy should abrogate the haemorrhagic complication in these patients. In intracranial neurosurgery, aspirin has been involved in an increased risk of postoperative intracerebral haematoma. In some cases it has been a contributing factor to the fatal issue.⁶²

Patients under aspirin and clopidogrel

When clopidogrel is added to aspirin, the bleeding rate is increased on average by 30–50%, but most of the studies have been conducted in cardiac surgery with full intraoperative heparinization for cardiopulmonary bypass. In this case, the transfusion rate is augmented from 51% (controls) to 73% (treatment) of the patients, and the number of blood units given increases from 1.6 to 3.0⁶³; the reoperation rate for haemostasis is increased from 1.6% to 9.8%. Clopidogrel intake during the last 4 days before CABG is an independent predictor of transfusions (odds ratio 4.22) and length of stay in intensive care unit (odds ratio 3.14).⁶⁴

In non-cardiac surgery, however, the situation is less obvious. In patients undergoing vascular, orthopaedic and visceral surgery after coronary stent implantation, a Mayo Clinic study showed that the transfusion rate is 38.5% in controls and 42.6% in patients under AP bi-therapy⁴²; the difference is insignificant. After transbronchial biopsy, the bleeding rate is very high (89%) in patients under clopidogrel compared to patients without AP treatment (3.4%), but no patient required transfusion, and each case was controlled by endoscopic route.⁶⁵ Case reports and small clinical series in visceral and vascular surgery have revealed an increase in surgical blood loss and transfusion rate, but not in morbidity or mortality. In neurosurgery, a short communication has recently described seven patients who developed fatal intracerebral haemorrhages associated with neurointerventional procedures and the use of clopidogrel and the anti-GP IIb/IIIa abciximab.⁶⁶ It appears therefore that the continuous use of clopidogrel during the perioperative period increases the surgical bleeding and the transfusion rate but not the morbidity or survival of the patients, with the exception of intracranial neurosurgery.

Platelet transfusion

Platelet transfusion may be indicated in cases of clopidogrel intake within 24 hours before an operation. The serum half-life of clopidogrel is 4 hours, but the platelets are irreversibly inhibited by the drug. However, since no drug is detectable in the serum beyond 3 half-lives, the platelet transfused beyond 12 hours after drug intake will not be blocked and will function normally. Among anti-GP IIb/IIIa, tirofiban (Aggrastat[®]) and eptifibatid (Integrilin[®]) have a serum half-life of 2 hours, but abciximab (ReoPro[®]) has a serum half-life of 23 hours. With the former, the risk of platelet inhibition disappears after 6 hours, whereas transfused platelets will be at least partially blocked by the latter when they are administered within 24 hours of the last dose.²⁸

PERIOPERATIVE AP DRUGS: MAINTAINING OR WITHDRAWING?

The recent data presented above tend to show that it has become imperative to modify the traditional standpoint of withdrawing patients from all AP drugs before surgery. The relative risks of keeping or removing this medication must be put in the balance. On the one hand are the risks of maintaining the AP drugs:

- average increase in haemorrhagic risk of 2.5–20% with aspirin, or 30–50% with aspirin plus clopidogrel; no increase in surgical morbidity or mortality linked to increased bleeding, except during intracranial neurosurgery;
- 30% increase in transfusion rate, but complication rate of red-blood-cell transfusion is 0.4%⁶⁷, and mortality linked to surgical severe or massive blood loss is $\leq 3\%$ ⁶⁸;

- ischaemic complication rate similar to the rate of stabilized CAD patients: non-fatal MI 2–6%, mortality 1–5%.³⁴

On the other hand are the risks of withdrawing the AP drugs:

- rebound effect with increased platelet adhesiveness, simultaneous with the increased platelet adhesiveness and decreased fibrinolysis of the acute-phase reaction to surgery;
- average postoperative MI rate of 30% during the re-endothelialization phase of coronary stents; MI mortality is 20–40%^{39,41,54};
- outside the intraoperative and immediate postoperative periods, cessation of AP drugs is associated with doubled MI and mortality rate in cases of acute coronary syndrome⁵³, increased risk of late DES thrombosis^{36,37,45}, 5–10 times increased rate of cardiac death.^{41,50,54}

It seems evident that the risks of cessation of AP drugs are much higher than the risks of maintaining them. Intraoperatively, it is easier to take care of increased bleeding than of an acute coronary thrombosis. Pending large prospective randomized studies on different AP regimens during non-cardiac surgery, we propose the following recommendations based on present knowledge and precaution principles (Figure 1):

- ASA is a lifelong therapy; it should not be stopped before surgery when it is prescribed as a secondary prevention after stroke, angina, MI or revascularization; as a primary prevention, it can be withdrawn 1 week before surgery.

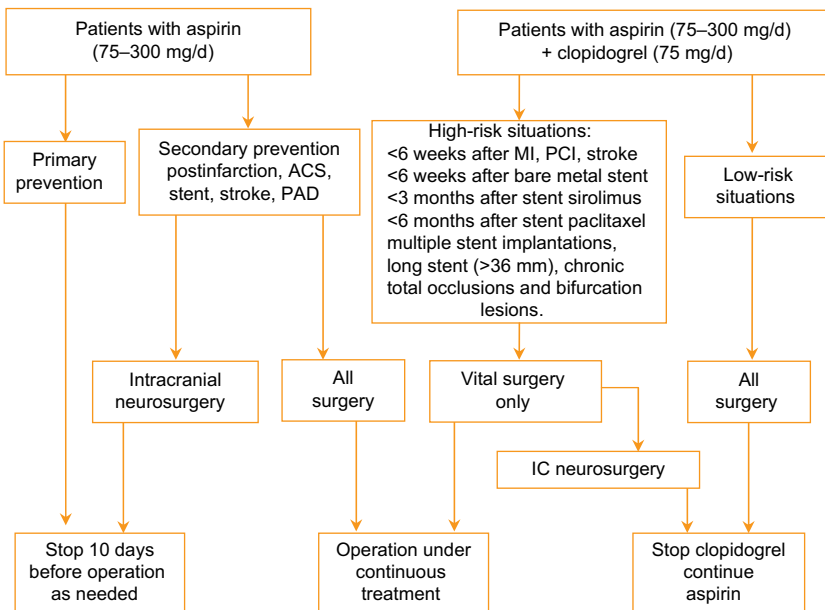


Figure 1. Algorithm for preoperative management of patients under anti-platelet therapy. ACS, acute coronary syndrome; PAD, peripheral arterial disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; IC, intracranial.

- If clopidogrel is prescribed for an unstable angina or during the re-endothelialization period of a stent, it should not be stopped before a non-cardiac procedure. This period lasts 2–4 weeks after simple dilatation, 6 weeks after BMS, 3–6 months after DES, and may be prolonged up to 1 year or more in unstable situations.
- In closed spaces, the least postoperative haemorrhage might have disastrous consequences, particularly in neurosurgery. Therefore, the attitude recommended in our institutions is to leave ASA but withdraw clopidogrel for 1 week before intracranial open-skull surgery; meanwhile, it would be safer to give low-molecular-weight heparin, although the degree of protection is inferior.⁵³ In the case of stereotaxic intracranial procedures, ASA should also be interrupted, but it would be more reasonable to postpone the operation until the patient can safely stop all AP medication.

During the year after discontinuation of clopidogrel, patients with DES present a significantly higher occurrence of MI or death than patients with BMS: 4.9% versus 1.3% ($P = 0.01$) in one study⁶⁹, or +38% ($P = 0.03$) for sirolimus-eluting stents and +16% ($P = 0.68$) for paclitaxel-eluting stents in a meta-analysis.⁷⁰ DES is clearly beneficial during the first 6 months when patients are still on clopidogrel.⁷¹ These recent data reinforce our attitude to maintain AP therapy in the perioperative period, even if the delay since PCI is relatively long.

THE PROBLEM OF REGIONAL ANAESTHESIA

The low-dose ASA therapy (≤ 300 mg/day) is not a contraindication to regional anaesthesia (RA), including neuraxial blockade.⁷² However, it is recommended to restrain from intraoperative heparinization in this case.⁷³ This attitude might create a problem in vascular surgery, where the administration of 100 U/kg heparin is usual before clamping an artery. There is no contraindication to administering heparin at the end of the procedure, but it should be stopped 12 hours before removing the epidural catheter. The intake of clopidogrel during the preceding week is a formal contraindication to any form of RA.²⁵

Frequently, the AP drugs are interrupted by the anaesthesiologist because he/she wants to perform a neuraxial blockade, on the basis that it is safer than a general anaesthesia in a patient suffering from CAD. Unfortunately, only a high thoracic epidural blockade ($>T6$ level) can induce a cardiac sympatholysis which increases coronary blood flow, decreases myocardial oxygen consumption (mVO_2)⁷⁴, and may reduce the incidence of postoperative MI linked to *demand ischaemia* (see above).^{75,76} Below the T6 level, the neuraxial blockade, alone or in combination with general anaesthesia, does not significantly reduce the cardiac risk^{77–79}; it does not modify mortality or infarction rate in a meta-analysis of 11 randomized trials (1173 patients).⁷⁵ In abdominal vascular surgery, one study revealed a decrease in cardiac complication rate with combined anaesthesia compared to general anaesthesia (10% versus 18%), but only in the subgroup of high-risk patients undergoing lengthy operations.⁷⁹ Neuraxial blockade might have an antithrombotic effect, with a slight reduction in the incidence of postoperative pulmonary embolism⁸⁰ and in the incidence of thrombosis in peripheral arterial reconstruction.⁸¹ One can argue that RA might reduce the intensity of the acute-phase reaction linked to surgery, and therefore decrease the risk of thrombosis on unstable plaques, but this hypothesis has not yet been demonstrated clinically.

Thus, the anaesthetist has to choose between two different attitudes: (1) keeping the protecting effect of clopidogrel on unstable plaques or uncovered stents and

proceeding with conventional general anaesthesia, or (2) stopping clopidogrel for at least 7 days before the operation in order to perform epidural or combined anaesthesia and benefit from its sympatholytic and analgesic effects. To the best of our knowledge, the protection of AP drugs is far more efficient than the effects of RA on arterial thrombosis and on the reduction of MI and cardiac death rates. Moreover, the intra-operative sympatholysis of epidural anaesthesia can also be realized with intravenous substances such as β -blockers, α_2 -agonists, and higher dosages of opioids.⁸² The only real disadvantage is a lower quality of postoperative analgesia and comfort for the patient. In conclusion, the risk/benefit ratio for patients under AP bi-therapy is in favour of continuing ASA and clopidogrel and thus renouncing neuraxial blocks.

URGENT OR SEMI-URGENT SURGERY

The dismal outcome of some pathologies – such as carcinomas, aneurysms, intracranial tumours, unstable fractures or infections requiring drainage – pleads in favour of a rapid surgical management. This might happen shortly after a PCI with stents or in a patient suffering from unstable angina. Three situations are possible:

1. The procedure must be performed within 24–48 hours. The patient should be placed under maximal medical therapy (β -blocker, aspirin, clopidogrel). It is useless to perform a coronary angiogram, because the results will not modify the therapeutic choice; if necessary, a simple transthoracic echocardiography will determine the ventricular function and rule out associated valvulopathy.
2. The non-cardiac surgery can wait for 2–3 weeks. In case of extremely unstable coronary flow, very proximal stenosis, and large area of threatened myocardium, it is possible to consider a PCI without stenting. Among 345 patients who underwent non-cardiac surgery within 60 days of balloon angioplasty without stenting, global mortality and non-fatal MI rates were 0.3% and 0.6%⁸³; only three major adverse cardiac events (one death and two MI) were noted in the 188 patients who underwent surgery within 2 weeks of PCI. When optimal 'stent-like' coronary dilatation is obtained with simple balloon angioplasty, the rates of major adverse cardiac events, repeat revascularization and death up to 12 months are homogeneously similar between PCI with and without immediate bare-metal stents.⁸⁴ Therefore, PCI without stenting may be a safe means of revascularization for patients who need an operation with minimal delay. With or without PCI, these patients must be treated with continuous perioperative β -blocker, statins and AP bi-therapy.
3. The operation can be delayed for 6 weeks. This is long enough to perform a PCI with placement of BMS and allow 4–6 weeks of double AP therapy. It would probably be safer to operate under the continuous protection of AP drugs. DES are contraindicated, because the operation would happen during the re-endothelialization phase, when the risk of stent thrombosis is the highest.

POSTOPERATIVE PCI

Since the greatest risk of ischaemia and infarction occurs during the first days after surgery, the treatment of chronic CAD (β -blocker, α_2 -agonist, anti-hypertensive agent) or unstable coronary syndrome (aspirin and clopidogrel) must be recommenced immediately after the operation. Routine monitoring of cardiac enzymes

is useful to unmask silent ischaemia, which is frequent during the postoperative period and predicts long-term mortality.⁸⁵ In case of STElevation, the patient should immediately be taken to the cath lab for a coronary angiogram and a PCI. Dilatation is mandatory, but stenting may be problematic because the early postoperative phase is characterized by an acute systemic inflammatory syndrome accompanied by a phase of blood hypercoagulability. Unfortunately, it is not possible to use GP IIb/IIIa inhibitors in the first 24–48 hours after surgery because of the risk of catastrophic bleeding. In this case, it might therefore be safer to refrain from stenting and proceed to a simple dilatation.

SUMMARY

Present data demonstrate that the risk of coronary thrombosis at AP drug withdrawal is much higher than the risk of surgical bleeding when maintaining them, except when haemorrhage supervenes in a closed space (skull, eye). After stroke, MI or coronary revascularization, ASA is a lifelong therapy that should never be stopped. Clopidogrel is mandatory as long as the endothelial covering is incomplete after intravascular instrumentation; the duration of therapy depends on the technique and type of stent used. Since surgery is characterized by increased platelet adhesiveness, AP drugs are particularly helpful when the risk of thrombosis is the highest.

ADDENDUM

Since the submission of the manuscript, new findings were published in the literature concerning the higher risk of late thrombosis of DES. These data tend to show that DES thrombosis carries a high mortality (19–45%), and that patency of DES is highly dependent on clopidogrel administration during the first year after implementation. Therefore, the updated AHA/ACC Science Advisory and the Society of Cardiovascular Angiography DES Task Force recommend 12 months of dual antiplatelet therapy after DES, and postponement of all elective operations for one year.^{86,87}

Practice points

- anti-platelet regimen should not be modified perioperatively
- low-dose aspirin (≤ 300 mg/d) in secondary prevention should never be stopped
- clopidogrel must be maintained in unstable coronary syndromes and during the re-endothelialization phase of stents (6–24 weeks)
- if haemorrhage in a closed space is feared, the combined treatment of aspirin–clopidogrel may be reduced to aspirin alone and heparin
- during the first 6–12 weeks after PCI and stent, only life-saving operations should be performed
- during PCI, the type of stent, if any, should be adapted to the presumed subsequent non-cardiac surgery

Research agenda

- to organize a large prospective randomized study of patients who require non-cardiac surgery in the early period after PCI and stent, comparing the outcome of combined aspirin and clopidogrel therapy with aspirin alone
- to test in a prospective randomized study the possibility of using low-molecular-weight heparin in place of clopidogrel in the perioperative period
- to conceive a screening test able to determine the patients who do not respond to anti-platelet drugs

REFERENCES

1. Steinbuhl SR, Berger PB, Mann JT et al. Early and sustained dual oral anti-platelet therapy following percutaneous coronary intervention. A randomized trial (CREDO). *JAMA: The Journal of the American Medical Association* 2002; **288**: 2411–2420.
2. Vicenzi MN, Meislitzer T, Heitzinger B et al. Coronary artery stenting and non-cardiac surgery – a prospective outcome study. *British Journal of Anaesthesia* 2006; **96**: 686–693.
- *3. Naghavi M, Libby P, Falk E et al. From vulnerable plaque to vulnerable patient. A call for new definitions and risk assessment strategies. Part I. *Circulation* 2003; **108**: 1664–1672.
4. Zipes DP & Wellens HJ. Sudden cardiac death. *Circulation* 1998; **98**: 2334–2351.
5. Dawood MM, Gupta DK, Southern J et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *International Journal of Cardiology* 1996; **57**: 37–44.
6. Landesberg G. The pathophysiology of perioperative myocardial infarction: Facts and perspectives. *Journal of Cardiothoracic and Vascular Anesthesia* 2003; **17**: 90–100.
7. Le Manach Y, Perrel A, Coriat P et al. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology* 2005; **102**: 885–891.
8. Giroud D, Li JM, Urban P et al. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *The American Journal of Cardiology* 1992; **69**: 729–732.
9. Poldermans D, Boersma E, Bax JJ et al. Correlation of location of acute myocardial infarct after non-cardiac vascular surgery with preoperative dobutamine echocardiographic findings. *The American Journal of Cardiology* 2001; **88**: 1413–1414.
- *10. Naghavi M, Libby P, Falk E et al. From vulnerable plaque to vulnerable patient. A call for new definitions and risk assessment strategies. Part II. *Circulation* 2003; **108**: 1772–1778.
11. Cooke GE, Liu-Stratton Y, Kerketch AK et al. Effect of platelet antigen polymorphism on platelet inhibition by aspirin, clopidogrel, or their combination. *Journal of the American College of Cardiology* 2006; **47**: 541–546.
12. Hoffmeister HM, Heller W & Seipel L. Activation markers of coagulation and fibrinolysis: alterations and predictive value in acute coronary syndrome. *Thrombosis and Haemostasis* 1999; **82**: 76–79.
13. Burke AP, Kolodgie FD, Farb A et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001; **103**: 934–940.
14. Mann J & Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. *Heart* 1999; **82**: 265–268.
15. Blake GJ & Ridker PM. Inflammatory biomarkers and cardiovascular risk prediction. *Journal of Internal Medicine* 2002; **252**: 283–294.
16. Peters RJ, Mehta SR, Fox KA et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003; **108**: 1682–1687.
17. Rodondi N & Cornuz J. Place de l'aspirine en prévention primaire des maladies cardio-vasculaires. *Revue Médicale Suisse* 2006; **2**: 646–651.
18. Antithrombotic Trialist's Collaboration. Collaborative meta-analysis of randomised trials of anti-platelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71–86.

19. Harrington RA, Becker RC, Ezekowitz M et al. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126**(3 supplement): 513S–548S.
20. Popma JJ, Berger P, Ohman EM et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126**(3 supplement): 576S–599S.
21. Neilipovitz DT, Bryson GL & Nichol G. The effect of perioperative aspirin therapy in peripheral vascular surgery: a decision analysis. *Anesthesia and Analgesia* 2001; **93**: 573–580.
22. Serruys PW, Kutryk MJB & Ong ATL. Coronary artery stents. *The New England Journal of Medicine* 2006; **354**: 483–495.
23. Yusuf S, Zhao F, Mehta SR, et al, CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *The New England Journal of Medicine* 2001; **345**: 494–502.
24. Mehta SR, Yusuf S, Peters RJ et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**: 527–533.
25. Weber AA, Braun M, Hohlfeld T et al. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. *British Journal of Clinical Pharmacology* 2001; **52**: 333–336.
26. Montalescot G, Barragan P, Wittenberg O et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *The New England Journal of Medicine* 2001; **344**: 1895–1903.
27. Sreeram GM, Sharma AD & Slaughter TF. Platelet glycoprotein IIb/IIIa antagonists: perioperative implications. *Journal of Cardiothoracic and Vascular Anesthesia* 2001; **15**: 237–240.
28. Genoni M, Zeller D, Bertel O et al. Tirofiban therapy does not increase the risk of hemorrhage after emergency coronary surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2001; **122**: 630–632.
29. Lev El, Patel RT, Maresh KJ et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention. The role of dual drug resistance. *Journal of the American College of Cardiology* 2006; **47**: 27–33.
30. Labarthe B, Théroux P, Angioi M & Ghitescu M. Matching the evaluation of the clinical efficacy of clopidogrel to platelet function tests relevant to the biological properties of the drug. *Journal of the American College of Cardiology* 2005; **46**: 638–645.
31. Wenaweser P, Dörrfler-Melly J, Imboden K et al. Stent thrombosis is associated with an impaired response to anti-platelet therapy. *Journal of the American College of Cardiology* 2005; **45**: 1748–1752.
32. Grewe PH, Deneke T, Machraoui A et al. Acute and chronic tissue response to coronary stent implantation: Pathologic findings in human specimen. *Journal of the American College of Cardiology* 2000; **35**: 157–163.
33. Ueda Y, Nanto S, Komamura K et al. Neointimal coverage of stents in human coronary arteries observed by angiography. *Journal of the American College of Cardiology* 1994; **23**: 341–346.
34. ACC/AHA guideline update for perioperative cardiovascular evaluation for non-cardiac surgery – executive summary. *Circulation* 2002; **105**: 1257–1267.
35. Sattler LF. Recommendations regarding stent selection in relation to the timing of noncardiac surgery postpercutaneous coronary intervention. *Catheterization and Cardiovascular Interventions* 2004; **63**: 146–147.
- *36. Iakovou I, Schmidt T, Bonizzoni E et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA: The Journal of the American Medical Association* 2005; **293**: 2126–2130.
37. Ong ATL, McFadden EP, Regar E et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *Journal of the American College of Cardiology* 2005; **45**: 2088–2092.
38. Bhatt DL, Fox KAA, Hacke W et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. The CHARISMA trial. *The New England Journal of Medicine* 2006; **354**: 1706–1717.
39. Kaluza GL, Joseph J, Lee JR et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *Journal of the American College of Cardiology* 2000; **35**: 1288–1294.
40. Posner KL, Van Norman GA & Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesthesia and Analgesia* 1999; **89**: 553–560.
41. Sharma AK, Ajani AE, Hamwi SM et al. Major noncardiac surgery following coronary stenting: when is it safe to operate? *Catheterization and Cardiovascular Interventions* 2004; **63**: 141–145.

42. Wilson SH, Fasseas P, Orford JL et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *Journal of the American College of Cardiology* 2003; **42**: 234–240.
43. Breen P, Lee JW, Pomposelli F & Park KW. Timing of high-risk vascular surgery following coronary artery bypass surgery: a 10-year experience from an academic medical centre. *Anaesthesia* 2004; **59**: 422–427.
44. Godet G, Riou B, Bertrand M et al. Does preoperative coronary angioplasty improve perioperative cardiac outcome? *Anesthesiology* 2005; **102**: 739–746.
45. McFalls EO, Ward HB, Moritz TE et al. Coronary artery revascularization before elective major vascular surgery. *The New England Journal of Medicine* 2004; **351**: 2795–2804.
46. Poldermans D, Boersma E, Bax JJ et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *The New England Journal of Medicine* 1999; **341**: 1789–1794.
47. Poldermans D, Bax JJ, Kertai MD et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003; **107**: 1848–1851.
48. Beving H, Zhao C, Albage A & Ivert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. *Blood Coagulation & Fibrinolysis* 1996; **7**: 80–84.
49. Fatah K, Beving H, Albage A et al. Acetylsalicylic acid may protect the patient by increasing fibrin gel porosity. Is withdrawing of treatment harmful to the patient? *European Heart Journal* 1996; **17**: 1362–1366.
- *50. Spertus JA, Kettelkamp R, Vance C et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement. *Circulation* 2006; **113**: 2803–2809.
51. McFadden EP, Stabile E, Regar E et al. Late thrombosis in drug-eluting coronary stents after discontinuation of anti-platelet therapy. *Lancet* 2004; **364**: 1519–1521.
52. Murphy JT & Brenda GF. Thrombosis of sirolimus-eluting coronary stent in the postanesthesia care unit. *Anesthesia and Analgesia* 2005; **101**: 971–973.
- *53. Collet JP, Montalescot G, Blanchet B et al. Impact of prior use or recent withdrawal of oral anti-platelet agents on acute coronary syndrome. *Circulation* 2004; **110**: 2361–2367.
- *54. Ferrari E, Benhamou M, Cerboni P & Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *Journal of the American College of Cardiology* 2005; **45**: 456–459.
- *55. Burger W, Chemnitz JM, Kneissl GD & Rucker G. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its preoperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. *Journal of Internal Medicine* 2005; **257**: 399–414.
56. Nutall GA, Santrach PJ, Oliver Jr WC et al. The predictors of red cell transfusions in total hip arthroplasties. *Transfusion* 1996; **36**: 144–149.
57. Manning BJ, O'Brien N, Aravindan S et al. The effect of aspirin on blood loss and transfusion requirements in patients with femoral neck fractures. *Injury* 2004; **35**: 121–124.
58. Nutall GA, Horlocker TT, Santrach PJ et al. Predictors of blood transfusions in spinal instrumentation and fusion surgery. *Spine* 2000; **25**: 596–601.
59. Lindblad B, Persson NH, Takolander R & Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind placebo-controlled, randomized study. *Stroke* 1993; **24**: 1125–1128.
60. Stage J, Jensen JH & Bonding P. Post-tonsillectomy haemorrhage and analgesics. A comparative study of acetylsalicylic acid and paracetamol. *Clinical Otolaryngology* 1988; **13**: 201–204.
61. Thurston AV & Briant SL. Aspirin and post-prostatectomy haemorrhage. *British Journal of Urology* 1993; **71**: 574–576.
62. Palmer JD, Sparrow OC & Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* 1994; **35**: 1061–1064.
63. Yende S & Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Critical Care Medicine* 2001; **29**: 2271–2275.
64. Chu MWA, Wilson SR, Novick RJ et al. Does clopidogrel increase blood loss following coronary artery bypass surgery? *The Annals of Thoracic Surgery* 2004; **78**: 1536–1541.
65. Ernst A, Eberhardt R, Wahidi M et al. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest* 2006; **129**: 734–737.
66. Qureshi A, Saad M, Zaidat OO et al. Intracerebral hemorrhages associated with neurointerventional procedures using a combination of antithrombotic agents including abciximab. *Stroke* 2002; **33**: 1916–1919.
67. Michlig C, Vu DH, Wasserfallen JB et al. Three years of haemovigilance in a general university hospital. *Transfusion Medicine (Oxford, England)* 2003; **13**: 63–72.

68. Kearon C & Hirsh J. Current concepts: Management of anticoagulation before and after elective surgery. *The New England Journal of Medicine* 1997; **336**: 1506–1511.
- *69. Pfisterer ME. Late clinical events related to late stent thrombosis after stopping clopidogrel: Prospective randomized comparison between drug-eluting versus bare-metal stenting. Highlights from the 55th Annual Scientific Sessions of the American College of Cardiology. Atlanta, 11–14 March 2006. *American Heart Journal* 2006; **151**: 1156–1172.
70. Camenzind E. Safety of drug-eluting stents: insights from meta-analysis. European Society of Cardiology Congress Reports, Hotline 1/707009. Barcelona, 3 september 2006.
71. Kaiser C, Brunner-La-Rocca HP, Buser PT et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitäts Trial (BASKET). *Lancet* 2005; **366**: 921–929.
72. Horlocker TT, Wedel DJ, Schroeder DR et al. Preoperative anti-platelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesthesia and Analgesia* 1995; **80**: 303–309.
73. Fox J. Spinal and epidural anesthesia and anticoagulation. *International Anesthesiology Clinics* 2001; **39**: 51–61.
74. Ollausson K, Magnusdottir H, Lurje L et al. Anti-ischemic and anti-anginal effects of thoracic epidural anesthesia versus those of conventional medical therapy in the treatment of severe refractory unstable angina pectoris. *Circulation* 1997; **96**: 2178–2182.
75. Beattie WS, Badner NH & Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesthesia and Analgesia* 2001; **93**: 853–858.
76. Rodgers A, Walker N, Schug S et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ (Clinical Research ed.)* 2000; **321**: 1493.
77. Norris EJ, Beattie C, Perler BA et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology* 2001; **95**: 1054–1067.
78. Rigg JR, Jamrozik K, Myles PS et al. Design of the multicenter Australian study of epidural anesthesia and analgesia in major surgery: the MASTER trial. *Controlled Clinical Trials* 2000; **21**: 244–256.
79. Park WY, Thompson JS & Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veteran Affairs cooperative study. *Annals of Surgery* 2001; **234**: 560–569.
80. Urwin SC, Parker MJ & Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. *British Journal of Anaesthesia* 2000; **84**: 450–455.
81. Christopherson R, Beattie C, Frank SM et al. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993; **79**: 422–434.
82. Liu SS, Block BM & Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* 2004; **101**: 153–161.
83. Brilakis ES, Orford JL, Fasseas P et al. Outcome of patients undergoing balloon angioplasty in the two months prior to noncardiac surgery. *The American Journal of Cardiology* 2005; **96**: 512–514.
84. Agostini P, Biondi-Zoccai GGL, Gasparini GL et al. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. *European Heart Journal* 2005; **26**: 881–889.
85. Landesberg G, Shatz V, Avopnik I et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *Journal of the American College of Cardiology* 2003; **42**: 1547–1554.
86. Grines CL, Bonow RO, Casey DE et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A Science Advisory from the American Heart Association, American College of Cardiology, Society of Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol* 2007; **49**: 734–739.
87. Hodgson JMcB, Stone GW, Lincoff AM et al. Late stent thrombosis: Considerations and practical advice for use of drug-eluting stents: A report from the Society for Cardiovascular Angiography and Interventions drug-eluting stent Task Force (Clinical Alert). *Catheter Cardiovasc Interv* 2007; **69**: 327–333.

Use of blood and blood products in trauma

Oliver Grottke* MD, MPH

Anaesthesiologist

Dietrich Henzler MD, PhD

Consultant Anaesthesiologist

Rolf Rossaint MD, PhD

Professor, Head of the Department of Anaesthesiology

University Hospital Aachen, Department of Anaesthesiology, Pauwelsstrasse 30, D-52074 Aachen, Germany

According to the global study of the burden of disease, violence and accidental injury account for 12% of deaths worldwide; 30–40% of trauma mortality is attributable to haemorrhage. The highly complex haemostatic system is severely impaired as a result of haemorrhagic shock, acidosis, hypothermia, haemodilution, hyperfibrinolysis, and consumption of clotting factors. Thus it is important to prioritize the prevention of the development of coagulopathy. Timely transfusion of red blood cells and plasma products becomes essential to restore tissue oxygenation, support perfusion, and maintain the pool of active haemostatic factors. The limits to this strategy to compensate for the loss of blood and coagulation factors are discussed. In the absence of international guidelines, there is an ongoing debate about a generally accepted treatment algorithm, mass transfusion protocols, and adverse events that have been observed as a result of transfusion. Thus many recommendations are based upon expert opinion rather than on evidence. In this chapter we address key issues of transfusions of red blood cells and plasma products in the acute control of bleeding in traumatized patients.

Key words: trauma; haemorrhage; haemostasis; coagulopathy; blood products.

Exsanguination after trauma has been identified to be the leading cause of early in-hospital mortality.^{1,2} Uncontrolled bleeding after trauma is usually caused by a combination of surgical and coagulopathic bleeding, requiring an interdisciplinary approach. On admission to hospital, 25–36% of trauma patients already show signs of coagulopathy.^{3,4}

Coagulopathic bleeding is multifactorial and includes dilution and consumption of coagulation factors, hypothermia, hypocalcaemia, acidosis and activation of fibrinolysis.

* Corresponding author. Tel.: +49 241 8088179; Fax: +49 241 8082406.
E-mail address: ogrottke@ukaachen.de (O. Grottke).

Surgical control of bleeding is unlikely to be successful if a combination of hypothermia, acidosis and coagulopathy – also called the ‘the lethal triad’ – is present.⁵

Hypothermia is an independent risk factor for bleeding and death⁶, causing an impairment of clotting, a reduction in the synthesis of coagulation factors, altered platelet function, and increased fibrinolysis.⁷ Since most laboratory tests – activated partial thromboplastin time (aPTT), prothrombin time (PT) – are performed at 37 °C, the effect of hypothermia on coagulation in the patient is often underestimated.⁸

Acidosis may develop as a result of reduction in tissue perfusion and consequent release of anaerobic metabolites, compromising the function of platelets and coagulation enzymes. Compared to pH 7.4, prothrombin activation at pH 7.0 is reduced by 70%.⁹ Thus the maintenance of tissue oxygenation and oxygen delivery remains one of the most important goals in the treatment of trauma victims.

Coagulopathy may further be aggravated by the infusion of large volumes during initial fluid resuscitation. The magnitude of dilution coagulopathy depends on the volume and the type of volume infused.¹⁰

The early recognition of haemorrhagic shock in the initial management phase is essential for the prevention of coagulopathy. Early signs of shock are¹¹:

- altered level of consciousness as a result of reduced cerebral perfusion;
- delayed capillary refilling, mottled skin as a consequence of reduced peripheral perfusion; and
- oliguria.

Analysis of lactate and base excess will further help to differentiate the severity of shock.^{12,13} A blood loss of <15% of total blood volume is usually well tolerated, while a loss of 30–40% will lead to haemorrhagic shock. A massive haemorrhage is defined as^{14,15}:

- loss of an entire blood volume equivalent within 24 h; or
- loss of 50% of blood volume within 3 h; or
- continuing blood loss at a rate of 150 mL/min; or
- continuing blood loss at a rate of 1.5 mL/kg/min over 20 min; or
- rapid blood loss leading to decompensation and circulatory failure, despite the support of blood products, volume replacement, and all accepted surgical and interventional treatments to stop bleeding.

For a targeted therapy it would be ideal to establish a relation between the volume of blood loss and reduction in coagulation factors and platelets. However, because of the high dynamic of blood loss, inter-individual variations in clotting factors, and the functionality of involved organ systems, this has not yet been accomplished.¹⁶ In order to preserve tissue oxygenation and maintain the pool of procoagulant factors, red blood cells (RBCs), plasma, and coagulation factors are transfused, but monitoring both the effects and the timing of the substitution is highly complicated. Therefore this review highlights selected issues in the transfusion of RBCs and plasma products.

BLOOD AND BLOOD COMPONENTS IN MASSIVE HAEMORRHAGE

Red blood cells (RBCs)

Transfusion of RBCs is a mainstay in trauma management. The concept of specific component therapy was developed during the 1960s. Whole blood units are separated

into RBCs, platelets and plasma, and these may be separated further (e.g. by cryoprecipitation). The advantage of this strategy is to allocate resources according to the needs of the individual patient, resulting in both economic and logistic benefits. One disadvantage is that, the substitution with plasma-free and thrombocyte-depleted RBCs can lead to coagulopathies at an earlier stage compared to the substitution of whole blood. An analysis from the Vietnam war revealed that the platelet count did not fall below $10^3/L$, despite massive transfusion of 6 L of whole blood.¹⁷ In contrast, 85% of patients receiving at least 10 units of RBCs developed thrombocytopenia.¹⁸ The use of whole blood continues in military settings because frozen components and platelets cannot be stored¹⁹, and large amounts of blood can be delivered in a timely manner even in the case of mass casualties.²⁰

Although it is known that the haematocrit influences coagulation, the specific effects are generally unknown. One mechanism is attributed to the margination of platelets. This means that platelets have to be pushed by red cells to the margin of the vessel to make contact with injured endothelial cells.²¹ Clinically, an acute reduction in the haematocrit leads to a prolongation of the bleeding time.²² In contrast, a moderate isolated reduction of haematocrit *in vitro* did not reveal an effect on thrombelastography except for the clot formation time.²³ Erythrocytes support thrombin generation²⁴ and maintain oxygen delivery, securing aerobic metabolism. However, there are well-described short-term and long-term negative effects of RBC transfusion encompassing haemolytic reaction and transmission of infectious diseases. With regard to trauma, RBC transfusion might also cause multiple organ failure (MOF) and increase the incidence of post-traumatic infections.^{25–28}

There is no randomized controlled trial (RCT) available comparing a liberal versus a restrictive transfusion regimen in trauma patients. Reanalysed data from the Transfusion Requirements in Critical Care trial showed that a restrictive regimen (transfusion trigger <7 g/dL) compared to a liberal regimen (transfusion trigger <10 g/dL) resulted in reduced numbers of RBCs transfused.^{29,30} Although the analysis did not show a beneficial effect of a restrictive transfusion regimen, reflected by similar incidences of MOF and post-traumatic infections, this could still be the case, since the study was not primarily designed or powered to answer this question. In contrast, an observational study with 15,534 patients by Malone et al revealed different results; in this trial 1703 trauma victims received on average 6.8 ± 6.7 units RBCs.³¹ After controlling for potential confounders – injury severity score (ISS), Glasgow coma score (GCS), shock variables, age, race – RBC transfusion was associated with increased mortality, admission to ICU and ICU length of stay. Until further RCTs adequately address these issues, it is generally agreed that the haemoglobin level in a bleeding patient should be maintained at 7–8 g/dL at least.³² Primary efforts in treating trauma victims should also include measures to reduce the need for RBC transfusion.

Platelets

Platelets are separated from whole blood by centrifugation or by apheresis. After preparation they can be stored for up to 5 days at room temperature (20–24 °C) with constant movement to prevent clotting. In massive bleeding, a relevant thrombocytopenia develops much later than plasma deficits, and will occur after the replacement of approximately 220% of circulating blood volume.³³ The decline of platelet count is individually different due to different capabilities for recruiting platelets from spleen and lung and the release of premature platelets from the bone marrow.

Since some patients even have high platelet counts despite ongoing bleeding, it is important to measure the platelet count repeatedly after admission. However, the number of platelets does not correlate with their ability to coagulate, and there are no practical methods for testing their activity.

A platelet count $<50 \times 10^9/L$ in a bleeding patient or a patient with a pre-existing coagulopathy is generally regarded as an indication to transfuse platelets. In most patients one aphaeresis concentrate will increase the platelet count by $20 \times 10^9/L$ (one platelet aphaeresis concentrate is approximately equivalent to a pool of 4–8 platelet concentrates).^{34,35} The adequacy of transfusion should be confirmed after 10–15 min post-transfusion³⁶, since ongoing bleeding, platelet consumption, or human leukocyte antibodies (HLA) may cause a lower increase in platelets than expected.³⁷ In the case of diagnosed HLA antibodies, only matched HLA platelets will be effective. The recovery rate of 5-day-old platelets is about 50%. Non-viable platelets are sequestered in the spleen.³⁸ No data are available about the time taken for these non-viable platelets to be removed from circulation in massive trauma. This might lead to falsely high platelet counts. Platelets become fully functional after 4 hours of administration.^{39,40}

A platelet count $>100 \times 10^9/L$ is usually sufficient and requires transfusion only if severe platelet dysfunction is present. In the absence of bleeding or coagulopathy, a low platelet count is not an indication to transfuse platelets.

Platelet inhibitors – acetylsalicylic acid, glycoprotein (GP) IIb/IIIa inhibitors, etc – severely reduce the capability of platelets to aggregate. In cardiac surgery it has been shown that the inhibitory platelet effect caused by clopidogrel doubles the need for RBCs and causes an eight-fold increase in the need for platelet substitution.⁴¹ In conclusion, the platelet count has to be interpreted in the specific clinical context.⁴²

Adverse reactions of platelet transfusion include transmission of infectious diseases, allergic reactions, transfusion-related lung injury (TRALI), graft-versus-host disease (GVHD), and bacterial infections, which might cause a septic platelet transfusion associated with a high mortality.⁴³

Fresh-frozen plasma (FFP)

Fresh-frozen plasma is human donor plasma separated from whole blood or obtained by plasmapheresis. It is frozen within 6–8 h after collection, stored at a temperature below -30°C , and must be thawed at 37°C before use. The volume of a typical unit contains 150–250 mL. FFP contains near-normal physiological levels of all plasma proteins – including procoagulant and inhibitor components of the coagulation cascade such as antithrombin – except FVIII, which rapidly decays.

Coagulation factors are diluted by approximately 15% during the preparation process with anticoagulant solution. During the freezing and thawing process further losses might occur. Also, the activity of coagulation factors depends on the donor's concentration of coagulation factors. Thus concentrations might vary between 60 and 140%. In contrast, solvent-detergent plasma (SD-FFP) contains pooled plasma from multiple donors, balancing the variations in factor concentrations.

According to guidelines from the American Society of Anesthesiologists (ASA), the indication for the use of FFP in trauma is a prolongation of prothrombin time and activated thromboplastin time of more than 1.5 times.³⁴ Furthermore, FFP is advised in patients with clinical signs of a bleeding coagulopathy, such as diffuse bleeding, massive transfusion, or disseminated intravascular coagulation (DIC). Other recommendations suggest transfusing FFP prophylactically after a certain number of units of RBCs have

been transfused.¹⁸ Nonetheless, there is no evidence for the dose that should be transfused, nor for the ratio of FFP to RBC that should be applied (1:1, 1:2 or 1:3). Also, it has not been proven whether prophylactic substitution of FFP prevents the development of coagulopathy or improves bleeding control^{44,45}, and there is no apparent correlation between the degree of bleeding and the total volume of plasma transfused.⁴⁶

Current recommendations on dosage are based on personal experience and expert opinion rather than on evidence. A dose of 10–15 mL/kg is widely accepted. However, if no volume deficit is present, patients with impaired cardiac or renal function might decompensate under volume overload.

Despite the lack of evidence, the number of FFP individually transfused has increased steadily over the last two decades in many countries.⁴⁷ Stanworth et al therefore did a systematic review of RCTs on the clinical effectiveness of the use of FFP.⁴⁸ From the 57 RCTs identified, only six could demonstrate a potential benefit with the use of FFP.

For life-threatening bleeding caused by warfarin overdosage, guidelines recommend the use of FFP only if prothrombin complex concentrate (PCC) is unavailable or contraindicated.¹⁰ It has been well documented that the effectiveness in correcting coagulopathy as reflected by the international normalized ratio (INR) and the levels of vitamin-K-dependent clotting factors is lower using FFP than using PCC.^{49,50} This is attributed to the level of factor IX in FFP, which is often too low to reach haemostatic concentrations. In order to achieve sufficient haemostatic concentrations of coagulation factors, the associated volume overload might become problematic. Besides, it has been shown that the administration of FFP is more prolonged than PCC. If PCC is not available, a dose of 15 mL/kg FFP is generally sufficient to correct warfarin-induced coagulopathy.^{51–53} Disadvantages of FFP usage include the time delay (turn-around time) of a minimum of 30 min for thawing and transport of FFP from the blood bank to the patient. In addition, FFP contain varying amounts of citrate or citric acid for anticoagulation purposes. Since citrate binds calcium, it is necessary to monitor the calcium concentration closely.⁵⁴ Special attention should be given to patients with reduced capacity to metabolize citrate, such as patients with hypothermia or liver failure. Moreover, the transfusion of FFP is associated with risk of TRALI and transmission of infectious diseases.

COAGULATION FACTORS

Recombinant activated factor VII (rFVIIa)

rFVIIa was originally developed as haemostatic agent for use in haemophilia patients who developed inhibitors to factor VIII or IX. Since its first approval 10 years ago by the US Food and Drug Administration (FDA), it has also been approved in Europe for factor VII deficiency and Glanzmann's thrombasthenia (GT) with past or present refractoriness to platelet transfusion. Haemostasis is induced by exogenous administration of pharmacological doses if rFVIIa plasma concentrations of ≥ 25 nmol/L is reached.⁵⁵ In these supraphysiological doses rFVIIa binds to the phospholipid structures of activated platelets at the site of injury and thereby directly activates factors IX and X. This augmentation of the coagulation process leads to the enhancement of thrombin (thrombin burst). The activation of platelets at the site of injury is the reason for a localized reaction of rFVIIa. Furthermore, it has been demonstrated that rFVIIa influences the fibrin structure in a dose-dependent manner by forming a tight fibrin structure which is resistant to premature lyses.⁵⁶

The efficacy of rFVIIa depends on the pH. An in-vitro study demonstrated that thrombin generation in response to rFVIIa administration was statistically significantly reduced during acidosis.⁹ On the other hand, no negative influence on the effectiveness of rFVIIa has been reported during hypothermia.⁵⁷

The first successful treatment of a nearly exsanguinated trauma patient with rFVIIa was reported in 1999.⁵⁸ Since then the numbers of case series and reports describing the still off-label use of rFVIIa in controlling massive haemorrhage is increasing.⁵⁹

Dutton et al published a large case series ($n = 81$) of patients with coagulopathic bleeding as a result of different causes, including traumatic haemorrhage and traumatic brain injury.⁶⁰ The use of rFVIIa in a dose range of 40–150 $\mu\text{g}/\text{kg}$ successfully stopped the coagulopathic bleeding in 75%. The Israeli Multidisciplinary rFVIIa Task Force reports another series with 36 trauma patients in whom the use of rFVIIa (dose range 100–140 $\mu\text{g}/\text{kg}$) prevented exsanguination in 72% of the cases.⁶¹ On the basis of their findings, they developed recommendations for the use of rFVIIa in uncontrolled haemorrhage, suggesting an initial dose of 120 $\mu\text{g}/\text{kg}$ followed by further doses (second dose of 100 $\mu\text{g}/\text{kg}$) if required after 15–20 min. Recently Boffard et al published the results from a multicentre, randomized, double-blind, placebo-controlled trial, stratifying for severe blunt and penetrating trauma.⁶² Patients were included in the study after receiving 6 units of RBCs and were randomized to obtain either three doses of rFVIIa (200, 100 and 100 $\mu\text{g}/\text{kg}$) or placebo. In addition, damage-control surgery to manage haemorrhage was performed. A significant reduction in the primary end-points, RBC units transfused, and need for massive transfusion (defined as >20 units of RBCs) was observed in patients with blunt trauma who survived for more than 48 h. The need for massive transfusion was reduced from 33% to 14% ($P = 0.03$). The incidence of acute respiratory failure was also significantly lower. Although a trend towards a reduced need for RBC transfusion and fewer mass transfusions was also observed in the group of penetrating injuries, this did not reach statistical significance. The incidence of adverse events was comparable between the placebo and rFVIIa groups, and no thromboembolic events were observed.

As a result of these findings, a European expert panel recommended the use of rFVIIa in blunt trauma with a starting dose of 200 $\mu\text{g}/\text{kg}$ (grade B).⁶³ In contrast, the use of rFVIIa was not recommended in penetrating trauma (grade B). However, in conclusion, the lack of data from randomized trials and the possibility of a publication bias in favour of successful case series were criticized. Furthermore, there is still a considerable lack of evidence about the timing of rFVIIa administration, the dosage, and the identification of the most suitable patients. At present, an international phase-III study is targeting to enrol 1500 patients with the aim to investigate, the effect of rFVIIa on mortality in trauma patients (CONTROL).

An algorithm for the use of rFVIIa based on the current evidence was developed to offer guidance for the practising physician (Figure 1). Most importantly, main factors additionally compromising coagulation (haematocrit, fibrinogen, platelets, pH) have to be corrected before rFVIIa is administered. After the application, close monitoring is advised for possible adverse thromboembolic events.

Fibrinogen and cryoprecipitate

The conversion from fibrinogen to fibrin is the final step in the coagulation cascade to clot formation. In a study enrolling 60 patients, Hiippala et al showed that fibrinogen is

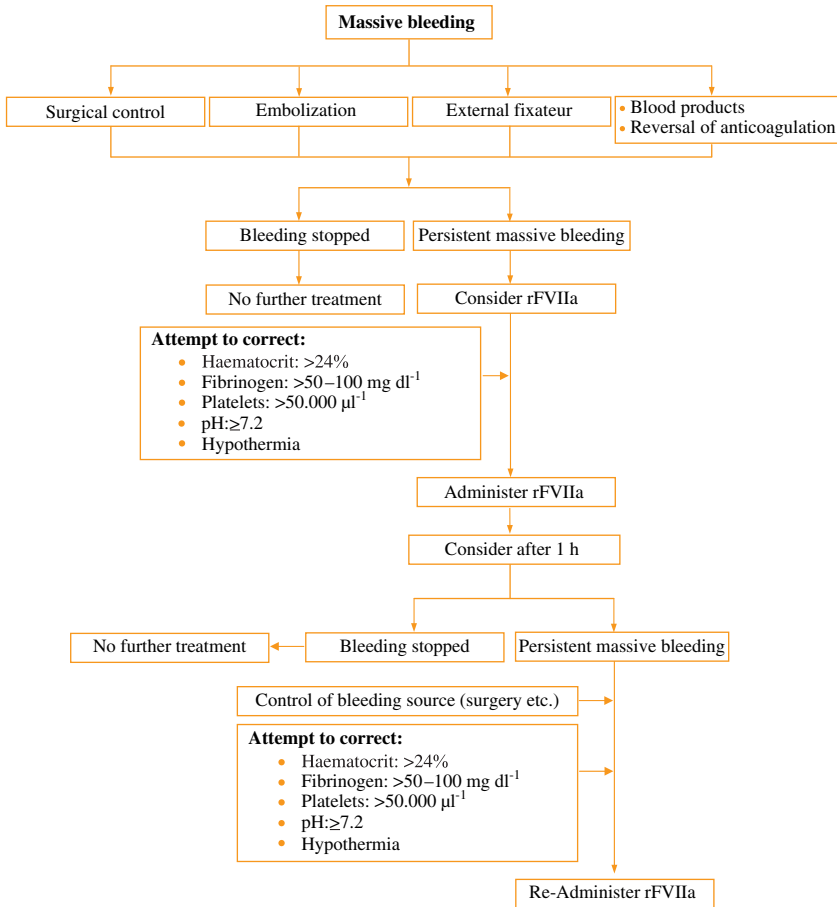


Figure 1. An algorithm for the use of recombinant activated factor VII (rFVIIa), developed by a European panel of experts modified from Ref. ⁶⁴

the first coagulation factor to reach critical concentrations when blood loss has reached 142% of the calculated blood volume.⁶⁴ Massive blood loss, large wound areas, and consumption and dilution of coagulation factors contribute to the decrease in fibrinogen level. The polymerization of fibrinogen is influenced by the interaction with colloids⁶⁵, and the clot firmness can additionally be reduced by concomitant hyperfibrinolysis. The impact of reduced fibrinogen concentration by dilution has been shown *in vitro* and *in vivo*.^{66,67} Using thrombelastography, Fries et al demonstrated that the impaired fibrin polymerization was reconstituted after the administration of fibrinogen.⁶⁷ Using electron microscopy, the exogenous administration of fibrinogen had a recovery effect on the thinner reticular network.

Despite the lack of evidence for the optimal dose of fibrinogen, different algorithms recommend the substitution of fibrinogen in bleeding patients if the level falls below 0.5–1.0 g/L.^{61,63} If the application of FFP in a bleeding patient is not sufficient to raise the fibrinogen plasma level to this concentration, the use of fibrinogen concentrate or cryoprecipitate might be indicated.

Fibrinogen concentrates are virally inactivated and are the treatment of choice for patients with inherited deficiencies of fibrinogen. On average, the adult dose is 2–3 g intravenously for acceptable levels to be achieved.

Cryoprecipitate contains factor VIII, von Willebrand factor (vWF), factor XIII, fibrinogen and fibronectin. It is the cryoglobulin fraction of FFP when thawed and centrifuged. On average, a dose of 2 mL/kg is used. One unit (10–20 mL) of cryoprecipitate should increase the fibrinogen level by 0.1 g/L. Since fibrinogen concentrates and cryoprecipitate are small in volume, both can be administered rapidly. If available, fibrinogen is the treatment of choice rather than cryoprecipitate.^{34,35,51} The effectiveness of substitution should be monitored by fibrinogen levels and clinical signs of bleeding. In addition, thrombelastography is useful to estimate the clot firmness. To our knowledge no specific adverse reactions except allergic reactions and anaphylaxis have been reported.

Prothrombin complex concentrate (PCC)

PCC contains the vitamin-K-dependent factors FII, FVII, FX and FIX. Because of the heterogeneity of available PCCs, the therapeutic amounts of factors vary (“four versus three factor concentrates”).⁶⁸ Most PCCs also contain heparin and proteins C and S, as well as protein Z of varying concentrations and antithrombin. All plasma products are virally inactivated and have a good safety record. The indications for the use of PCC are a fast reversal of oral anticoagulation with warfarin or a known deficiency of the vitamin-K-dependent factors in potentially life-threatening bleeding. The substitution should be supplemented by intravenous vitamin K to induce the endogenous synthesis of vitamin-K-dependent factors. Dosing recommendations are controversial, suggesting either an adjustment according to INR⁶⁹ or standard doses regardless of INR.⁷⁰ It seems reasonable to monitor the effect of PCC therapy based on the results of INR and the clinical effect.⁷¹

Well-known adverse effects include thromboembolism (coronary and cerebral arteries) and disseminated intravascular coagulation, which appear in a dose-dependent manner.^{72,73} Moreover PCC is very expensive. Therefore, PCC should be applied only after careful assessment of the individual benefits and risks. The clinical diagnosis or a history of heparin-induced thrombocytopenia (HIT) are contraindications to using PCC.

Single-factor therapy

The substitution of mono-component factor therapy is required for correcting coagulopathy in patients with congenital factor deficiencies such as haemophilia A or B or von Willebrand's disease (vWD). Patients with massive haemorrhage and no history of isolated coagulation factor deficits do not require single-factor replacement.

PHARMACOLOGICAL AGENTS TO SUPPORT COAGULATION

Antifibrinolytic drugs

In trauma patients both hypofibrinolytic and hyperfibrinolytic states have been described^{74–76}, depending on the time of assessment and the severity of the trauma. Ideally antifibrinolytic drugs should only be used in the evidence of hyperfibrinolysis.

However, RCTs have also shown a blood-sparing effect of aprotinin and tranexamic acid in cardiac surgery in prophylactical use.^{77,78}

Antifibrinolytic agents currently in use are the serin protease inhibitor aprotinin and the synthetic analogues ϵ -aminocaproic acid (6-aminohexanoic acid, EACA) and tranexamic acid (TXA).⁷⁹ Aprotinin is a naturally occurring polypeptide which unspecifically inhibits serine proteases such as plasmin, trypsin, kallikrein and others; it is isolated from bovine lung. The antifibrinolytic mechanism is mediated by the reversible formation of inhibitor complexes. Since aprotinin inhibits plasmin it interferes neither with fibrin-bound plasmin nor with plasminogen. The activity of aprotinin is expressed in kallikrein inactivator units (KIU). 1 KIU is defined as the amount of aprotinin that decreases the activity of two biological kallikrein units by 50%.⁸⁰ To inhibit plasmin, plasma concentrations of 125 KIU/mL aprotinin are usually needed.⁸¹ Although different dose regimens have been proposed, the most common is to administer a loading dose of 1–2 million KIU followed by a continuous infusion of 100,000–200,000 KIU/h.⁸² A rapid redistribution in the extracellular space leads to an initial decrease in plasma concentration. Finally, aprotinin is metabolized in a biphasic pattern with metabolism in the proximal renal tubes.⁸³

After the administration of aprotinin, anaphylactic reactions have been observed, induced by the circulating foreign polypeptide. The re-exposure to aprotinin within 6 months increases the risk of developing a severe anaphylactic reaction in up to 4.5% of cases.⁸⁴ A recently published international observational prospective study by Mangano et al showed that the use of aprotinin in cardiac surgery was associated with an increased risk of renal failure and myocardial infarction.⁸⁵ A propensity score case-control comparison of aprotinin and tranexamic acid from Karkouti et al also concluded that the use of aprotinin might be associated with an increased risk of renal dysfunction.⁸⁶ Based on those studies, the US FDA advises limiting the use of aprotinin to situations where the clinical benefit of reduced blood loss outweighs the potential risks.⁸⁷ Furthermore, the FDA recommends to carefully monitor for adverse events.

EACA and TXA are competitive inhibitors of plasminogen activation. TXA is about 10 times more potent than EACA *in vitro*, with sustained antifibrinolytic activity.⁸⁸

A systematic review of RCTs from Henry et al investigated whether the use of antifibrinolytics in elective surgery reduces the need for allogenic transfusion.⁸⁹ Aprotinin reduced the rate of blood transfusion by 30% (RR = 0.70; 95%CI: 0.64–0.76), whereas TXA reduced the rate by 34% (RR = 0.66; 95%CI: 0.54–0.81). In contrast, EACA showed no significant reduction in the need for RBC transfusion (RR = 0.48; 95%CI: 0.19–1.19). This review also revealed that most data were obtained from RCTs using aprotinin leading to a potentially publication bias. Whether or not antifibrinolytic drugs could contribute to reducing the need for RBC transfusion in trauma patients has not yet been sufficiently investigated.⁹⁰

The CRASH-II trial (clinical randomization of antifibrinolytics in significant haemorrhage) is currently investigating the effects of TXA in a large cohort of 20,000 trauma patients.⁹¹

Desmopressin (DDAVP)

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of vasopressin. It increases plasma levels of both FVIII and vWF from endothelial storage sites in healthy individuals as well as in deficient patients.⁹² Desmopressin is an effective

treatment in bleeding patients with congenital bleeding disorders, such as haemophilia and certain vWF disease type.⁹³ Plasma concentrations of factor VIII and vWF are up to quadrupled after administration.⁹⁴ Results from different studies using desmopressin after the use of aspirin to reduce haemorrhage after coronary artery surgery bypass grafting are not conclusive.^{95–97}

In a meta-analysis, Carless et al showed the effect of desmopressin in elective surgery.⁹⁸ Neither the blood loss (WMD = -114.3 mL; 95%CI: -258 to 30.2 mL) nor the need for RBC transfusion (WMD = -0.35 units; 95%CI: -0.7 to 0.01 units) was reduced. The authors concluded that there is no evidence for the administration of desmopressin to reduce the need for blood transfusion in the absence of congenital disorders. Furthermore, there are no data available for its use in trauma patients.

SUMMARY

Coagulopathy after trauma is multifactorial and remains a challenge requiring an interdisciplinary approach. Most effort should be made to prevent the development of coagulopathy. Once the distortion of the complex haemostatic coagulation has developed, a clear strategy is essential for overcoming coagulopathy. Clinical assessment should supplement close laboratory monitoring to identify the cause of persistent bleeding. To preserve tissue oxygenation and maintain the pool of coagulation factors in massive haemorrhage, RBCs, FFP and platelets remain the mainstay of therapy. Supplementing fibrinogen or PCC should be undertaken only on the individual patient's need. The use of rFVIIa in trauma has been shown to be beneficial in blunt injuries, but further data on dosage, timing, and indication are urgently needed. Pharmacological treatments to support coagulation are effective in reducing the need for RBCs transfusion in different clinical settings, but insufficient data are available on the use of these substances in trauma.

Practice points

- hypothermia and acidosis severely impair coagulation and should be avoided or corrected, respectively
- use of RBCs and plasma products should be adapted to clinical monitoring and laboratory tests of haemostasis, including thrombelastography
- FFP is generally required when the PT or aPTT are more than 1.5 times the normal value
- fibrinogen and cryoprecipitate may be used if the fibrinogen level is lower than 0.5–1.0 g/L
- PCC is recommended in a bleeding patient with warfarin anticoagulation
- before the administration of rFVIIa, surgical and interventional methods to control haemorrhage should be performed; in case of persistent bleeding, an initial dose of 200 µg/kg rFVIIa is recommended and should be followed by 1–2 repeated doses of 100 µg/kg if necessary
- adjuvant therapy with antifibrinolytics might be useful in certain cases of haemorrhage bleeding and hyperfibrinolysis

REFERENCES

1. Gofrit ON, Leibovici D, Shapira SC et al. The trimodal death distribution of trauma victims: military experience from the Lebanon War. *Military Medicine* 1997; **162**: 24–26.
2. Sauaia A, Moore FA, Moore EE et al. Epidemiology of trauma deaths: a reassessment. *The Journal of Trauma* 1995; **38**: 185–193.
3. MacLeod JB, Lynn M, McKenney MG et al. Early coagulopathy predicts mortality in trauma. *The Journal of Trauma* 2003; **55**: 39–44.
4. Brohi K, Singh J, Heron M & Coats T. Acute traumatic coagulopathy. *The Journal of Trauma* 2003; **54**: 1127–1230.
5. Ferrara A, MacArthur JD, Wright HK et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *American Journal of Surgery* 1990; **160**: 515–518.
6. Krishna G, Sleigh JW & Rahman H. Physiological predictors of death in exsanguinating trauma patients undergoing conventional trauma surgery. *The Australian and New Zealand Journal of Surgery* 1998; **68**: 826–829.
7. Yoshihara H, Yamamoto T & Mihara H. Changes in coagulation and fibrinolysis occurring in dogs during hypothermia. *Thrombosis Research* 1985; **37**: 503–512.
8. Douning LK, Ramsay MA, Swygert TH et al. Temperature corrected thrombelastography in hypothermic patients. *Anesthesia and Analgesia* 1995; **81**: 608–611.
9. Meng ZH, Wolberg AS, Monroe 3rd DM & Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *The Journal of Trauma* 2003; **55**: 886–891.
10. Rossaint R, Cerny V, Coats TJ et al. Key issues in advanced bleeding care in trauma. *Shock* 2006; **26**: 322–331.
11. American College of Surgeons. *Advanced Trauma Life Support (ATLS) for Doctors*. 7th edn. Chicago, IL: American College of Surgeons, 2004.
12. Abramson D, Scalea TM, Hitchcock R et al. Lactate clearance and survival following injury. *The Journal of Trauma* 1993; **35**: 584–588.
13. Davis JW, Parks SN, Kaups KL et al. Admission base deficit predicts transfusion requirements and risk of complications. *The Journal of Trauma* 1996; **41**: 769–774.
14. Erber WN. Massive blood transfusion in the elective surgical setting. *Transfusion and Apheresis Science* 2002; **27**: 83–92.
15. Harvey MP, Greenfield TP, Sugrue ME & Rosenfeld D. Massive blood transfusion in a tertiary referral hospital. Clinical outcomes and haemostatic complications. *The Medical journal of Australia* 1995; **163**: 356–359.
16. Spahn D & Rossaint R. Coagulopathy and blood component transfusion in trauma. *British Journal of Anaesthesia* 2005; **95**: 130–139.
17. Simmons RL, Collins JA, Heisterkamp CA et al. Coagulation disorders in combat casualties. I. Acute changes after wounding. II. Effects of massive transfusion. 3. Post-resuscitative changes. *Annals of Surgery* 1969; **169**: 455–482.
18. Faringer PD, Mullins RJ, Johnson RL & Trunkey DD. Blood component supplementation during massive transfusion of AS-I red cells in trauma patients. *The Journal of Trauma* 1993; **34**: 481–485.
19. Repine TB, Perkins JG, Kauvar DS & Blackborne L. The use of fresh whole blood in massive transfusion. *Trauma* 2006; **60**: 59–69.
20. Mabry RL, Holcomb JB, Baker AM et al. United States Army Rangers in Somalia: an analysis of combat casualties on an urban battlefield. *The Journal of Trauma* 2000; **49**: 515–528.
21. Eberst ME & Berkowitz LR. Hemostasis in renal disease: pathophysiology and management. *The American Journal of Medicine* 1994; **96**: 168–179.
22. Valeri CR, Cassidy G, Pivacek LE et al. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. *Transfusion* 2001; **41**: 977–983.
23. Bombeli T & Spahn DR. Updates in perioperative coagulation: physiology and management of thromboembolism and haemorrhage. *British Journal of Anaesthesia* 2004; **93**: 275–287.
24. Peyrou V, Lormeau JC, Herault JP et al. Contribution of erythrocytes to thrombin generation in whole blood. *Thrombosis and Haemostasis* 1999; **81**: 400–406.

25. Moore FA, Moore EE & Sauaia A. An independent risk factor for postinjury multiple organ failure. *Archives of Surgery* 1997; **132**: 620–624.
26. Sauaia A, Moore FA, Moore EE et al. Multiple organ failure can be predicted as early as 12 hours after injury. *The Journal of Trauma* 1998; **45**: 291–303.
27. Claridge JA, Sawyer RG, Schulman AM et al. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *The American Surgeon* 2002; **68**: 566–572.
28. Edna TH & Bjerkeset T. Association between blood transfusion and infection in injured patients. *The Journal of Trauma* 1992; **33**: 659–661.
29. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *The New England Journal of Medicine* 1999; **340**: 409–417.
30. McIntyre L, Hebert PC, Wells G et al. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *The Journal of Trauma* 2004; **57**: 563–568.
31. Malone DL, Dunne J, Tracy JK et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *The Journal of Trauma* 2003; **54**: 898–907.
32. Croce MA, Tolley EA, Claridge JA & Fabian TC. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. *The Journal of Trauma* 2005; **59**: 19–23.
33. Hiiipala S. Replacement of massive blood. *Vox Sanguinis* 1998; **74**: 399–407.
34. American Society of Anesthesiologists Task Force on Blood Component Therapy. Practice guidelines for blood component therapy. *Anesthesiology* 1996; **84**: 732–747.
35. College of American Pathologists. Practice parameters for the use of fresh frozen plasma, cryoprecipitate and platelets. *JAMA: The Journal of the American Medical Association* 1994; **271**: 777–781.
36. Ness P, Braine H, King K et al. Single-donor platelets reduce the risk of septic platelet transfusion reactions. *Transfusion* 2001; **41**: 857–861.
37. Murray DJ, Pennell BJ, Weinstein SL & Olson JD. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. *Anesthesia and Analgesia* 1995; **80**: 336–342.
38. Slichter SJ. Relationship between platelet count and bleeding risk in thrombocytopenic patients. *Transfusion Medicine Reviews* 2004; **18**: 153–167.
39. British Committee for Standards in Haematology Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003; **122**: 10–23.
40. George JN, Woolf SH, Raskob GE et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **1**: 3–40.
41. Chen L, Bracey AV, Radovancevic R et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *The Journal of Thoracic and Cardiovascular Surgery* 2004; **128**: 425–431.
42. Hardy JF, de Moerloose P, Samama CM & Members of the Groupe d'Interet en Hemostase Perioperative. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Canadian Journal of Anaesthesia* 2006; **53**: 40–58.
43. Kleinman S, Chan P & Robillard P. Risks associated with transfusion of cellular blood components in Canada. *Transfusion Medicine Reviews* 2003; **17**: 120–162.
44. Martin DJ, Lucas CE, Ledgerwood AM et al. Fresh frozen plasma supplement to massive red blood cell transfusion. *Annals of Surgery* 1985; **202**: 505–511.
45. Popovsky MA. Transfusion-related acute lung injury. In Popovsky MA (ed). *Transfusion Reactions*. Bethesda: AABB Press, 2001.
46. Phillips TF, Soulier G & Wilson RF. Outcome of massive transfusion exceeding two blood volumes in trauma and emergency surgery. *The Journal of Trauma* 1987; **27**: 903–910.
47. Wallace EL. Monitoring the nation's blood supply. *Transfusion* 2003; **43**: 299–301.
48. Stanworth SJ, Brunskill SJ, Hyde CJ et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *British Journal of Haematology* 2004; **126**: 139–152.
49. Makris M, Greaves M, Phillips VS et al. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thrombosis and Haemostasis* 1997; **77**: 477–480.
50. Nitu IC, Perry DJ & Lee CA. Clinical experience with the use of clotting factor concentrates in oral anticoagulation reversal. *Clinical and Laboratory Haematology* 1998; **20**: 363–367.

51. O'Shaughnessy DF, Atterbury C, Bolton Maggs P et al. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology* 2004; **126**: 11–28.
52. Menzebach A, Cassens U, Van Aken H & Booke M. Strategies to reduce perioperative blood loss related to non-surgical bleeding. *European Journal of Anaesthesiology* 2003; **20**: 764–770.
53. Makris M & Watson HG. The management of coumarin-induced over-anticoagulation. *British Journal of Haematology* 2001; **114**: 271–280.
54. Cote CJ, Drop LJ, Hoaglin DC et al. Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: effects of infusion rate, duration, and treatment with calcium chloride. *Anesthesia and Analgesia* 1988; **67**: 152–160.
55. Hedner U. Mechanism of action of factor VIIa in the treatment of coagulopathies. *Seminars in Thrombosis and Hemostasis* 2006; **32**: 77–85.
56. He S, Blomback M, Jacobsson Ekman G & Hedner U. The role of recombinant factor VIIa (FVIIa) in fibrin structure in the absence of FVIII/FIX. *Journal of Thrombosis and Haemostasis* 2003; **1**: 1215–1219.
57. Martinowitz U, Holcomb JB, Pusateri AE et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *The Journal of Trauma* 2001; **50**: 721–729.
58. Kenet G, Walden R, Eldad A & Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; **354**: 1879.
59. O'Connell KA, Wood JJ, Wise RP et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA: The Journal of the American Medical Association* 2006; **18**: 293–298.
60. Dutton RP, Cooper C, Jones A et al. Daily multidisciplinary rounds shorten length of stay for trauma patients. *The Journal of Trauma* 2003; **55**: 913–919.
61. Martinowitz U & Michaelson M. The Israeli Multidisciplinary rFVIIa Task Force Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *Journal of Thrombosis and Haemostasis* 2005; **3**: 640–648.
62. Boffard KD, Riou B, Warren B et al. NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *The Journal of Trauma* 2005; **5**: 8–15.
63. Vincent JL, Rossaint R, Riou B et al. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding - a European perspective. *Critical Care* 2006; **10**: R120.
64. Hiippala ST, Myllyla GJ & Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesthesia and Analgesia* 1995; **81**: 360–365.
65. Innerhofer P, Fries D, Klingler A & Streif W. In vivo effect of haemodilution with saline on coagulation. *British Journal of Anaesthesia* 2002; **89**: 934–939.
66. Fries D, Innerhofer P, Reif C et al. The effect of fibrinogen substitution on reversal of dilutional coagulopathy: an in vitro model. *Anesthesia and Analgesia* 2006; **102**: 347–351.
67. Fries D, Krismer A, Klingler A et al. Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. *British Journal of Anaesthesia* 2005; **95**: 172–177.
68. Hanley JP. Warfarin reversal. *Journal of Clinical Pathology* 2004; **57**: 1132–1139.
69. Preston FE, Laidlaw ST, Sampson B & Kitchen S. Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *British Journal of Haematology* 2002; **116**: 619–624.
70. Evans G, Luddington R & Baglin T. Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. *British Journal of Haematology* 2001; **115**: 998–1001.
71. Erber WN & Perry DJ. Plasma and plasma products in the treatment of massive haemorrhage. *Best Practice & Research. Clinical Haematology* 2006; **19**: 97–112.
72. Kohler M. Thrombogenicity of prothrombin complex concentrates. *Thrombosis Research* 1999; **95**: 13–17.
73. Lusher JM. Thrombogenicity associated with factor IX complex concentrates. *Seminars in Hematology* 1991; **28**: 3–5.
74. Enderson BL, Chen JP, Robinson R & Maull KI. Fibrinolysis in multisystem trauma patients. *The Journal of Trauma* 1991; **31**: 1240–1246.

75. Engelman DT, Gabram SG, Allen L et al. Hypercoagulability following multiple trauma. *World Journal of Surgery* 1996; **20**: 5–10.
76. Risberg B, Medegard A, Heideman M et al. Early activation of humoral proteolytic systems in patients with multiple trauma. *Critical Care Medicine* 1986; **14**: 917–925.
77. Casati V, Sandrelli L, Speziali G et al. Hemostatic effects of tranexamic acid in elective thoracic aortic surgery: a prospective, randomized, double-blind, placebo-controlled study. *The Journal of Thoracic and Cardiovascular Surgery* 2002; **123**: 1084–1091.
78. Mossinger H, Dietrich W, Braun SL et al. High-dose aprotinin reduces activation of hemostasis, allogeneic blood requirement, and duration of postoperative ventilation in pediatric cardiac surgery. *The Annals of Thoracic Surgery* 2003; **75**: 430–437.
79. Mahdy AM & Webster NR. Perioperative systemic haemostatic agents. *British Journal of Anaesthesia* 2004; **93**: 842–858.
80. Franck M & Sladen RN. Drugs to prevent and reverse anticoagulation. *Anesthesiology Clinics of North America* 1999; **17**: 799–811.
81. Hoffmann H, Siebeck M, Thetter O et al. Aprotinin concentrations effective for the inhibition of tissue kallikrein and plasma kallikrein in vitro and in vivo. *Advances in Experimental Medicine and Biology* 1989; **247**: 35–42.
82. Royston D, Bidstrup BP, Taylor KM & Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987; **2**: 1289–1291.
83. Porte RJ & Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002; **62**: 2193–2211.
84. Dietrich W, Spath P, Ebell A & Richter JA. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *The Journal of Thoracic and Cardiovascular Surgery* 1997; **113**: 194–201.
85. Mangano DT, Tudor IC, Dietzel C, Multicenter Study of Perioperative Ischemia Research Group & Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *The New England Journal of Medicine* 2006; **354**: 353–365.
86. Karkouti K, Beattie WS, Dattilo KM et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; **46**: 327–338.
87. <http://www.fda.gov/cder/drug/infosheets/hcp/aprotininhcp.htm> [accessed October 2006].
88. Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs* 1985; **29**: 236–261.
89. Henry DA, Moxey AJ, Carless PA et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2001; **1**: CD001886.
90. Coats T, Roberts I & Shakur H. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database of Systematic Reviews* 2004. CD004896.
91. www.crash2.lshtm.ac.uk [accessed October 2006].
92. Levi M, Cromheecke ME, de Jonge E et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354**: 1940–1947.
93. Mannucci PM. Treatment of von Willebrand's Disease. *The New England Journal of Medicine* 2004; **351**: 683–694.
94. Mannucci PM. Hemostatic drugs. *The New England Journal of Medicine* 1998; **23**(339): 245–253.
95. Gratz I, Koehler J, Olsen D et al. The effect of desmopressin acetate on postoperative hemorrhage in patients receiving aspirin therapy before coronary artery bypass operations. *The Journal of Thoracic and Cardiovascular Surgery* 1992; **104**: 1417–1422.
96. Sheridan DP, Card RT, Pinilla JC et al. Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Canadian Journal of Surgery* 1994; **37**: 33–36.
97. Pleym H, Stenseth R, Wahba A et al. Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesthesia and Analgesia* 2004; **98**: 578–584.
98. Carless PA, Henry DA, Moxey AJ et al. Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2004; **1**: CD001884.

Estimating the cost of blood: past, present, and future directions

Aryeh Shander* MD, FCCP, FCCM

Chief, Department of Anesthesiology and Critical Care and Hyperbaric Medicine
Medical Director, New Jersey Institute for the Advancement of Bloodless Medicine and Surgery
Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631, USA

Axel Hofmann ME

Medical Society for Blood Management, A-2361 Laxenburg, Austria

Hans Gombotz MD

Chief

*Department of Anesthesiology and Intensive Care, General Hospital Linz, Krankenhausstrasse
9, A-4021 Linz, Austria*

Oliver M. Theusinger MD, PhD

Research Associate

Institute of Anesthesiology, University Hospital Zurich, Switzerland

Donat R. Spahn MD, FRCA

Professor and Chairman

*Department of Anesthesiology, University Hospital Lausanne (Chuv), Rue du Bugnon 46,
CH-1011 Lausanne, Switzerland*

Understanding the costs associated with blood products requires sophisticated knowledge about transfusion medicine and is attracting the attention of clinical and administrative health-care sectors worldwide. To improve outcomes, blood usage must be optimized and expenditures controlled so that resources may be channeled toward other diagnostic, therapeutic, and technological initiatives. Estimating blood costs, however, is a complex undertaking,

* Corresponding author. Tel.: +1 201 894 3238; Fax: +1 201 894 0585.

E-mail addresses: aryeh.shander@ehmc.com (A. Shander), axel.hofmann@bloodmanagement.org (A. Hofmann), Hans.gombotz@akh.linz.at (H. Gombotz), oliver.theusinger@usz.ch (O.M. Theusinger), donat.spahn@usz.ch (D.R. Spahn).

surpassing simple supply versus demand economics. Shrinking donor availability and application of a precautionary principle to minimize transfusion risks are factors that continue to drive the cost of blood products upward. Recognizing that historical accounting attempts to determine blood costs have varied in scope, perspective, and methodology, new approaches have been initiated to identify all potential cost elements related to blood and blood product administration. Activities are also under way to tie these elements together in a comprehensive and practical model that will be applicable to all single-donor blood products without regard to practice type (e.g., academic, private, multi- or single-center clinic). These initiatives, their rationale, importance, and future directions are described.

Key words: blood; blood products; economics; transfusion.

INTRODUCTION

Delivering health care at a reduced cost while maintaining or improving the quality of care is a challenging global quest. From societal and payer perspectives, collecting and maintaining a blood supply free of potentially infectious viruses, bacteria, and prions is enormously costly.¹ For example, detecting HIV and HCV with nucleic-acid testing (NAT) exceeds the acceptable limit to gauge cost-effectiveness benchmark (\$80,000 per-quality of life-year [QALY] gained) by 72- to 105-fold.² With blood donor pools shrinking owing to population aging, restrictions on blood donor eligibility^{3,4}, and operative procedures rising to increase demand, recruitment efforts need to be reinforced to replace deferred donors, resulting in increasing incremental cost for each additional unit donated.⁵ Implementing appropriate checks to ensure that transfusions are administered safely without laboratory, clerical, managerial, screening, or administration errors⁶ is associated with costs still to be estimated.⁷

Transfusion-related adverse events, both short- and long-term, are among the costliest contributors to health care expenditures.⁸ Costs associated with long-term consequences are among the hardest to quantify.^{4,9-14} Pharmacoeconomic analyses are complex because of uncertainties with calculating the probabilities of illness, projecting future outcomes, and discounting.¹ Lost wages and adverse events that have an impact on quality of life add to indirect costs of blood product transfusions, but these factors have rarely been incorporated into quantitative cost-analyses.^{15,16} Adding increased liability and regulatory (i.e., haemovigilance) issues to the list, blood product costs will continue to trend upward.

Despite the increasing cost of blood, transfusion practices remain quite liberal^{17,18}, variable from institution to institution¹⁹, and are often inappropriate.^{20,21} The percentage of costs attributable to inappropriate blood transfusion ranges between 9% and 44%.²¹ Frequent transfusions are also linked to poorer outcomes, including increased patient mortality^{22,23}, a higher incidence of nosocomial infections²⁴, multi-organ failure^{25,26}, and increased length of hospital and ICU stays.^{23,27,28}

How is the cost of blood to individuals, health-care providers, and society determined? Unless all contributing cost elements are accounted for, beginning with blood collection, continuing through pretransfusion preparation and transfusion administration, and lasting throughout follow-up, the cost of blood is very likely to be underappreciated. That premise forms the rationale and basis of this manuscript. Past attempts to ascertain the cost of blood and the shortcomings of studies will be reviewed, as well as the progress made by the Society for the Advancement of Blood Management (SABM) toward estimating what blood really costs from a societal perspective. We

also examine our expectations about how these estimates and descriptions of cost elements can serve as benchmarks and roadmaps that institutions worldwide can use to examine their processes, optimize blood usage, and save valuable resources.

PAST: EVALUATIONS OF BLOOD AND TRANSFUSION COSTS

Studies on the economics of blood have been conducted in oncology patients^{29–32}, in the perioperative and ICU setting^{21,33}, in neonates³⁴, and in patients who require chronic transfusions (e.g., sickle cell anaemia, thalassaemia, chronic renal disease).^{35–37} Cost analyses have been used to compare red blood cell (RBC) administration to transfusion alternatives.^{15,36,38,39} Although these studies provide useful information, several shortcomings exist. First, transfusion-related costs are captured with varying degrees of rigor. Second, many studies estimate costs associated with RBC transfusions but may not consider costs associated with the handling of specialty products. Third, although a societal perspective is preferred because a more complete picture is provided, the health-care providers' perspective is more commonly applied.¹

The simplest way to examine blood costs is by cost per unit of allogeneic RBCs (Table 1). However, even when considering this least common denominator, cost estimates are not easily compared because the premises and perspectives adopted by each investigator differ. From there, establishing the cost of blood becomes increasingly more complex. One reason is that allogeneic RBC transfusions comprise only 75% of blood product transfused. Over 11 different types of RBC products are available (including washed white blood cell [WBC]-reduced, filtered WBC-reduced, pediatric units, frozen-deglycerolized cells, CMV-negative) whose incremental costs are considerably higher than the base unit.²⁹ For example, examining several recent price lists from US and European blood services, the cost of specialty-processed blood units can be 40%–230% higher per unit than that of a standard, nonleukodepleted packed RBC unit.

Studies about the cost of blood have typically separated direct and indirect costs and further divided these into variable and fixed costs. Direct variable expenses are those associated with materials that vary with usage, i.e., the RBC units and administration sets, costs of labour and of laboratory tests.³¹ Overhead (generally a fixed cost) contributed 46% to the price of a unit of blood, whereas material, fixed, and variable labour costs each contributed 19%, 18%, and 17% to total costs, respectively, as estimated by Cremieux et al.³² In addition to the cost of the blood unit itself, laboratory test kits, administration materials, institutional overhead, and labour costs of handling blood are incorporated into most models.^{29,32} Some have included costs associated with blood wastage, especially blood collected for autologous use, which contributes significantly.^{40,41}

PRESENT: ELEMENTS CONTRIBUTING TO BLOOD COST

Blood costs will generally depend on the number of steps it takes to deliver the transfused unit; simply stated, more steps translate into higher costs. Process flow diagrams (e.g., Figure 1) can help illustrate the complexities involved in administering blood transfusions after the decision to transfuse is made.^{31,32} Although it generates valuable information, this approach does not include cost elements incurred before a unit is ready to be transfused, i.e., beginning at donor recruitment and continuing through collection, screening, blood processing, donor notification, transport from the collection facility to the transfusion center, and costs related to inventory.⁴²

Table 1. Prior estimates of costs of allogeneic red blood cells.

Citation (reference year \$)	Acquisition Cost (% of total)	Total Cost per Unit ^a	Methods
Forbes et al. 1991(1989 \$) ²⁹	37%	\$350.49	Total: Direct costs included acquisition, handling, laboratory, administration in a mixed population.
Etchason et al. (1995)(1992 \$) ⁴⁰	50% (includes labor and equipment for collection)	\$269.00	Direct: Labor, equipment, infectious tests, processing, inventory management, and compatibility tests in mixed surgical population. Indirect: Discarded, crossover cross-match, treatment of complications Total: Direct + Indirect
Cantor et al. ^b (1998)(1995 \$) ³¹	15%	\$429.22 ^c	Outpatient transfusions administered to oncology patients. A process flow model was used to determine costs per step. Direct: Direct variable (blood, supplies, tests) + direct fixed (clinical personnel, managerial, facility, capital) Total: average direct + indirect fixed (support services, facility and general administration) unit costs for solid tumor, hematologic tumor patients
Creemieux et al. (2000)(1998 \$) ³²	18%	\$780.59	Outpatient transfusions administered to oncology patients. A process flow model was used to determine costs per step. Direct: Direct material (products, kits, administration sets, screening for viruses) + variable direct labor (personnel) + fixed (administrators) Total: average direct + overhead unit costs for solid tumor, hematologic tumor, and complex patients

^a Adjusted for inflation from (reference year \$) to (2005 \$) based on Consumer Price Index for Medical Care Services per the US Department of Labor, Bureau of Labor Statistics available at: www.bls.gov Accessed 10/26/06.

^b May be significantly underestimated since Cantor et al.³¹ provided costs per 2 units of RBC transfused, and the cost per unit may actually be higher than that of 2 units divided in half.

^c Non-bone marrow transplant solid tumor estimate.

Cost elements associated with long-term adverse events may be missed. Interdependence among tasks and how one sector affects another are almost never considered. For example, if screening for viruses after donation becomes more stringent, more donors will be deferred. This can lead to the need to increase recruitment efforts to replace deferred donors, counselors to work with donors who are made aware they have a virus, reporting requirements, stepped-up haemovigilance efforts, look-back notifications, etc.

Seeking to develop an all-inclusive reference methodology that can be used to calculate the societal cost of single-donor blood components, applicable across

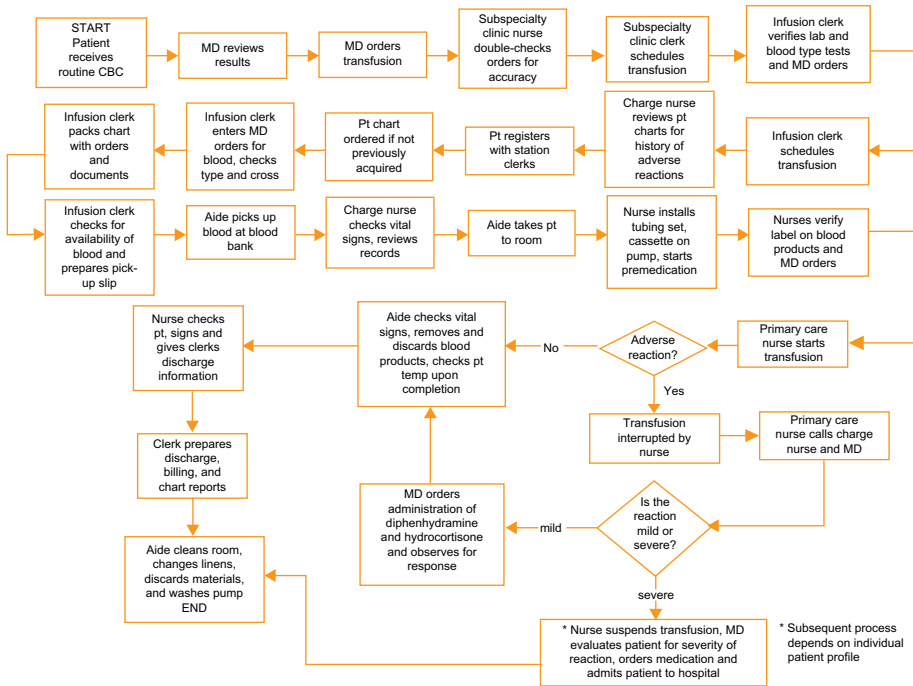


Figure 1. Process flow of outpatient RBC transfusion administration. This flow chart is part of a larger process, comprising a limited portion of cost elements (i.e., Steps 7 & 8 in Figure 2). (Reprinted from Cantor, et al³¹ with permission from the American Society of Clinical Oncology.)

institutions, payer types, delivery systems, and countries, SABM organized the first cost-of-blood consensus conference (COBCON 1). Consisting of 17 experts from blood collection facilities, government agencies, academia, hospitals, and practitioners in transfusion medicine, the group used the model first proposed by the Lewin Group⁴³ and then defined key cost elements and interdependencies associated with whole blood collection, transfusion processes, and follow-up (Figure 2).⁴²

Direct costs of preparing and delivering blood products distinct from simple allogeneic RBC units can also affect the bottom line.⁴⁰ For example, allogeneic RBC units are the least costly to prepare (Table 2), but pose higher risks of viral and bacterial transmission and immunological consequences. Predonated autologous units are 33% more expensive per unit to collect and process and only eliminate some, but not all, blood transfusion risks. Although 33% seems a reasonable premium to improve upon blood safety⁴⁰, predonated autologous blood costs escalate dramatically when wastage of unused units is included. Modeling surgical procedures in which up to 66% of self-donated blood was wasted⁴¹, incremental costs of substituting autologous for allogeneic units were \$68 to \$4,783 per unit. The highest costs were associated with the lowest probability of using the predonated autologous units. In another study, of all the blood collected for autologous or directed donations, 52%-57% (~4% of the US blood supply) was discarded, even after correcting for blood transferred into the allogeneic blood supply.⁴⁴ The COBCON panel recognized the importance of accounting for discarded units in their working model.

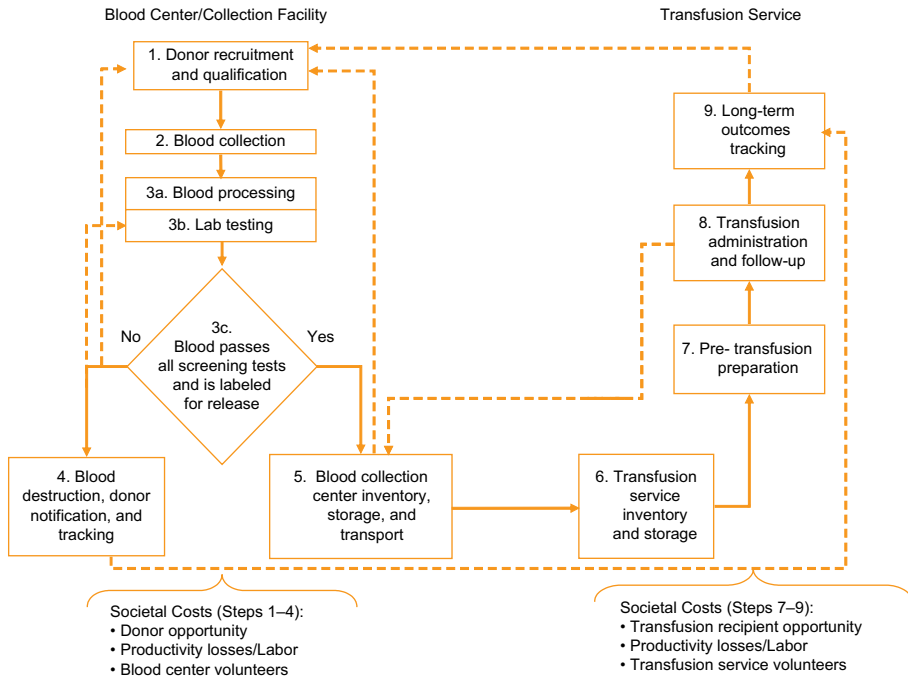


Figure 2. Blood collection and transfusion flow chart. (Reprinted from the Cost of Blood Consensus Conference participants⁴² with permission from Elsevier.

Additional steps and costs are incurred if collected blood is processed into specialty blood products.²⁹ Leukodepletion by filtration or washing to avoid alloimmunization and other immunomodulatory effects^{45,46} adds to the direct costs of blood (\$39/unit adjusted for inflation to 2005 [AFI₂₀₀₅]).⁴⁷ Dzik and colleagues estimated this cost to total \$600 million (\$667 million AFI₂₀₀₅) in the US alone.⁴⁸ Given that standards for implementing such testing differ from country to country, a tool is needed to estimate these costs according to the standards that apply.

Table 2. Direct costs of collecting, testing, and processing autologous and allogeneic blood.

Item	Cost per Unit (US Dollars)		% Higher
	Autologous	Allogeneic	\$ (Auto-Allo)/\$ Allo
Collection	129.42	84.91	51.9
Infectious disease testing	24.27	24.27	0
Blood processing and inventory management	28.16	25.03	12.5
Compatibility testing	16.19	16.19	0
Total	198.04	149.80	32.2

Adapted from Etchason, et al⁴⁰

COST-EFFECTIVENESS EVALUATIONS OF BLOOD TRANSFUSIONS

Strategies to improve blood safety are resource-intensive. In some cases, pharmacoeconomic principles have been applied and cost-effectiveness studies performed to help determine whether society can afford to pay for the added safety benefit. Value is assigned to variables measured in health units, i.e., years of survival gained, number of infections avoided, or hospital length of stay (LOS) shortened. In cost-utility analyses, incremental benefits are adjusted to common units, i.e., the quality-adjusted life year (QALY).¹ If the dollar value assigned to QALYs exceeds \$50,000 to \$80,000, the intervention will typically be less acceptable from a financial perspective.

Autologous versus allogeneic blood

In one of the first economic studies comparing predonated autologous to allogeneic blood, the number of dollars per QALY varied from \$235,000 to over \$23 million, causing the authors to conclude that autologous donations were not cost-effective.⁴⁰ Birkmeyer and colleagues examined low transfusion risk versus high transfusion risk surgical procedures and estimated dollars per QALY ranging from \$40,000 (high risk) to over \$1 million (low risk) for autologous donations, reflecting that wasted units produce the highest costs.⁴⁹ These investigators also demonstrated that autologous programs in patients undergoing coronary artery bypass graft (CABG) surgery would cost between \$508,000 and \$909,000 per QALY. An even higher estimate of \$26 million to \$300 million per QALY was projected to prevent one HIV transmission in pregnant women delivering term infants using an autologous blood program.⁵⁰ Unfortunately, none of these estimates compare favourably to cost-effectiveness benchmarks, ranging from \$6,000 to \$79,000 per QALY for procedures such as CABG in coronary artery diseased patients with angina, cervical cancer screening every 4 years, adjuvant chemotherapy for breast cancer, kidney or heart transplants, treatment with captopril for mild to moderate hypertension, or hemodialysis for end-stage renal disease.⁵¹

A cost analysis of autologous blood processed using cell-salvage machines versus allogeneic blood transfusions indicated that cost equivalence of the two products would be reached if using autologous blood could theoretically reduce the hospital LOS by between 0.3 and 2 days.⁵² Their analyses did not include infection risk or other immune consequences; larger studies to determine cost-equivalence were recommended. Blumberg and Heal⁵³ considered the cost associated with managing immunological sequelae and calculated total hospital charges associated with giving 1 to ≥ 3 allogeneic transfusions were \$5,000 to \$11,000 higher than those in patients who received up to 5 units of autologous blood. The public health impact of autologous blood and whether it is worth the incremental cost warrants further study.

White blood cell reduction

Leukodepletion has had positive effects on mortality in specific patient populations⁵⁴⁻⁵⁶ and some transfusion reactions⁵⁷, and it is mandatory practice in many countries, however, this practice has still not been universally adopted.^{47,58} Cost-effectiveness evaluations of leukoreduced blood products have revealed that the cost per QALY due to leukoreduction is highly sensitive to infection risk, ranging from \$2,470 if risk is high (1.85 relative risk) to \$3.4 million if there is no infection risk. Thus, in order for this

practice to be fiscally acceptable, leukoreduction must actually reduce the incidence of infection, cancer, or other immunologic-related consequences.

This issue of benefit has been intensely debated.^{59–61} In the US, universal WBC reduction is not mandated but is estimated to be applied in the vast majority of hospitals. Many reports assert that leukoreduction is cost-effective^{53,62,63}, and that LOS or hospital charges are sufficiently reduced to justify higher costs.⁵⁸

Older blood

Especially in critically ill patients, deleterious effects and increased mortality have been associated with administration of older blood.⁶⁴ Decreased deformability of RBC membranes owing to oxidation, diminished 2,3-DPG levels impairing O₂ delivery, decreased pH, diminished oxygen-carrying capacity, decreased number of viable cells per unit, and an increase in inflammatory cytokines released by contaminating leukocytes are some of the characteristics that RBCs express when nearing their expiration date.⁶⁵ Any of these characteristics can negatively affect the anticipated benefit of a transfusion, especially in a critically ill patient.⁶⁶ Additionally, the incidence of nosocomial infections may increase with the length of RBC storage.^{67,68}

To date, no studies have attempted to quantitate cost or outcomes of providing fresh versus older blood. Since 2 of 14 million units per year outdate⁶⁹, it may be very costly for society to adopt strategies to direct fresh blood supplies to certain populations. Improving the efficiency of blood banking systems, or expanding geographical areas served by individual blood banks to better utilize existing blood inventories may be warranted but will certainly add many cost elements.

More stringent blood collection and testing paradigms

More stringent and extensive screening during blood collection has made the blood supply safer, but has also made blood more difficult to acquire. Donors are more often rejected because of increasingly stringent standards.^{70,71} The Food and Drug Administration (FDA) final rule on testing human blood for transmissible infections⁷² does *not* require screening of autologous blood provided that the collection center does not transfer blood collected for autologous use to the allogeneic blood supply. Cost was one of the FDA's primary considerations when deliberating the recommendation to test all blood.^{72,73}

The use of NAT for detection of viral RNA or DNA has added to blood costs.⁷⁴ Individual unit testing reduces risk^{75,76} and the reagents used are relatively inexpensive; however, indirect costs, especially the impact of higher donor disqualification or discard rates, have not been examined. The concept of testing pooled batches versus individual units may reduce costs somewhat, but could also result in false negatives with potentially harmful outcomes.⁷⁷ The QALYs per infection detected have been estimated at \$1.3 and \$1.8 million dollars for pooled versus individual testing, respectively.^{78,79}

Pathogen inactivation

Processes and chemical agents designed to eliminate viral and bacterial infectious risks have been in clinical development as a potential alternative to NAT screening.⁸⁰ Many unknowns related to disposal, neutralization, processing, and logistical or administrative tasks exist.^{81,82} It will be important for cost estimates of untreated blood to be robust so that these new technologies can be adequately evaluated.

Quality management and quality control

Technologic improvements for administering transfusions and monitoring transfusion practices have been made^{83,84}, including safeguards against clerical and management errors that can lead to adverse events.⁸⁵⁻⁸⁷ Blood collection, blood-banking, administering transfusions, and all blood-related activities are highly regulated and require adequate training, standard operating procedures and protocols, and stringent controls.⁸⁸ Under the umbrella of administrative monitoring are processes for lookback-notifications of transfused patients for the risks of contracting HIV and HCV, estimated to cost approximately \$14.50 (AFI₂₀₀₅) for each transfused patient.⁸⁹ Computerized systems are necessary to manage the vast quantity of transfusion-related data. Development and implementation of efficient computer systems contribute to overhead costs.

COSTS OF TRANSFUSION-RELATED ADVERSE EVENTS

Medical implications

Any evaluation of the cost of blood must consider the costs of treating and managing adverse events that can result from transfusions, of which there are many.^{4,10} The costs of some adverse consequences found in the literature provide some perspective (Table 3).⁹⁰⁻⁹⁵ The probability of sustaining an adverse event is usually factored into any decision-tree analysis; most risks occur with low probability.⁹⁶ For example, death immediately following or directly linked to transfusions is rare, resulting from haemolysis, pulmonary injury, bacterial contamination, graft versus host disease (GVHD), delayed haemolysis, and infusion of incorrect, contaminated, or damaged product.^{4,14,97} Transfusion-acquired infections, also rare, still represent a risk that will never be 100% eliminated.^{4,12,98-100} Of all transfusion-related fatalities reported to the FDA (1986-1991), 16% to 26% were related to bacterial contamination.¹⁰⁰ Viruses that are undetectable due to lack of screening tests also remain a health concern.⁴

Although the immunologic consequences of blood transfusion are incompletely understood, these can result in poorer outcomes.^{4,10,45,46,54,101,102} Other severe events, e.g., transfusion-related acute lung injury (TRALI), transfusion-associated GVHD, or transfusion errors may go undiagnosed and are left underreported^{14,103-105}, and their costs are not always attributed to transfusion. Some of the more commonly recognized related expenditures addressed in cost studies include treating nosocomial infections^{106,107}, increased hospital charges to manage the immunological consequences of allogeneic versus autologous transfusions⁵³, increased costs due to prolonged hospital and ICU lengths of stay^{27,99,107,108}, lost time from work¹⁶, costs of treating serious medical sequelae (sepsis, acute respiratory distress syndrome, systemic inflammatory response syndrome [SIRS])^{108,109}, and increased mortality.¹⁰⁹ Chelation therapy for iron overload secondary to chronic transfusions is also costly.³⁵

Legal implications

An important consideration often omitted from cost of blood studies involves the costs of litigation and damages awarded. Transfusion medicine is a very highly regulated sector of our medical system, and legal issues surrounding patient and donor consent and litigation relating to transfusion adverse events can have significant economic consequences. A few pertinent examples of negligence convictions incurring monetary

Table 3. Estimated costs of managing transfusion-related sequelae.

Potential Event	Costs of Events	References
HIV infection (CD4 count <200)	\$318/month	McCarthy et al ⁹⁰ ; Hellinger et al ⁹¹
Symptomatic AIDS	\$6,970/month	
Lifetime cost HIV	\$119,000	
Hepatitis infection and related sequelae	\$1,106/1st year (acute) \$2,340/hospitalization (acute) \$3,085/1st year (chronic) \$287/year > 1st year (chronic) \$1,700/year for cirrhosis \$20,900/hepatocellular carcinoma (one-time cost)	Sonnenberg et al ⁹² ; Wong et al ⁹³
Lost earnings/ productivity	\$74/day for patient \$133/day for employer	Denton ¹⁵ ; Barnett et al ¹⁶
Bacterial infection	\$12,900–\$14,000/per event	Sonnenberg et al ⁹² ; Carson et al ⁹⁴
Hemolytic transfusion reactions	\$100 (minor)–\$1,000 \$112,578 (fatal)	Sonnenberg et al ⁹² ; Denton ¹⁵ ; Birkmeyer et al ⁴⁹
Nosocomial infection	\$16,309 (converted from Euros) \$66,302 higher hospital costs (2-fold) than noninfected controls in patients with end-stage renal disease	Liu et al ¹⁰⁶ ; Orsi et al ¹⁰⁷
Chelation therapy for iron overload	\$12,719 to \$24,845 per patient/year	Wayne et al ³⁵
ICU costs	\$1,246/day (fixed + variable; converted from £)	Dickie et al ⁹⁵
Hospital costs	\$1,551/day × 10.3 days nontransfused; \$1,682/day × 16.7 days transfused in colorectal cancer patients	Vamvakas et al ²⁸
Sepsis	\$877/day Canadian (survivors) \$1,724/day Canadian (non-survivors) \$22,100/case	Letarte et al ¹⁰⁸ ; Angus et al ¹⁰⁹
Sequelae related to immunomodulation	\$5,000–\$11,000 incremental hospital charges if allogeneic vs autologous	Blumberg & Heal ⁵³

damages, each up to \$500,000, include missing documentation, inadequate quality controls, lack of shipping records or temperature controls, insufficient tests performed to ensure safety, type and cross-match errors, and inadequately executed informed consent. In some cases, criminal prosecutions have resulted, which would further impact costs from society's perspective.^{86,110}

Haemovigilance

Systems in place to ensure the safety of the blood supply vary considerably from country to country.¹¹¹ At the present time, no information exists about what

haemovigilance systems cost in terms of personnel and administration or what their economic impact might be. The ability to input haemovigilance costs by country or region as applicable would seem to be more useful than any broad generalization.

FUTURE: COBCON 2

The importance of establishing a baseline cost of any particular blood product from which all future cost-effectiveness analyses could be determined cannot be overemphasized. In light of the foregoing discussion, we can now unequivocally assert that arriving at a dollar figure for the cost of blood is a complex undertaking. Moreover, for such a baseline to be meaningful, it should be customized for individual circumstance. Building upon the work product initiated by COBCON 1, a subset of individuals (COBCON 2) continue to pursue development of a widely applicable and practical cost-calculating tool, using activity-based cost methodology previously described.¹¹² From a societal perspective, the cost of blood should include the following:

1. Cost incurred to donors
2. Cost of producing blood components for transfusion
3. Cost of transfusion logistics and preparation within hospitals
4. Cost of administering and monitoring actual transfusions
5. Cost of treating adverse transfusion events
6. Cost of treating transfusion transmitted disease
7. Cost of litigation (claims of contaminated victims)
8. Cost of lost productivity
9. Cost of organizing and maintaining nationwide/continental haemovigilance systems.

Using the economic expertise available to COBCON 1 (Axel Hofmann, Medical Society for Blood Management), a basic cost-equation has been constructed (Figure 3) and, at present, is being populated with actual dollar values. A preliminary estimate of more than \$1,400 per unit (based on European transfusion volumes in 2004) has been calculated, representing a minimum to which costs associated with elements 1, 4, 6, 7, 8, and 9 listed above have yet to be added. Even though these costs still need to be incorporated, the dollar figure is nearly twofold more than any previous cost of blood estimate AFI₂₀₀₅ (Table 1).

The data emerging from COBCON 2 confirm what the experts from COBCON 1 suspected, namely, that the cost of blood has been seriously underestimated in previous studies. This knowledge could stimulate change in the way that transfusions are used and how transfusion alternatives are evaluated. It may also help administrators justify appropriation of funds to reduce and optimize transfusion usage.

Economic opportunities afforded by blood conservation strategies

The principles underlying optimization of blood usage include correcting anaemia before surgery, avoiding or minimizing intraoperative blood loss, and, with an understanding of the individual's physiological tolerance of anaemia, use more restrictive transfusion triggers when appropriate.¹¹³ Considering these principles, the Austrian Study Group for the Advancement of Blood Management (formally SABM-Austria), in the name of the Austrian Federal Structural Fund and the Federal Ministry of Health and Women, conducted a benchmarking evaluation to predict savings that might

$$C_{txn} = \frac{C_1X_1+C_2X_2+C_3X_3+C_4X_4+C_5X_5+C_6X_6+C_7X_7+C_8X_8+C_9X_9}{X_4} = \frac{\sum_{n=1}^9 C_n X_n}{X_4}$$

Where:

C_{txn} = total cost per unit transfused from a societal perspective

X_4 = total number of units transfused

C_1X_1 = average cost incurred per donor x number of donations = total donor cost

C_2X_2 = average cost per unit produced x units produced = total production cost

C_3X_3 = average cost per unit prepared for transfusion x units prepared = total hospital transfusion preparation cost

C_4X_4 = average cost of administering per unit transfused x units transfused = total hospital cost of administering transfusion

C_5X_5 = average cost per adverse transfusion event (short-term) x events = total cost of treating adverse events

C_6X_6 = average cost per transfusion-transmitted case of illness (long-term) x cases = total cost of transfusion-transmitted illness

C_7X_7 = average cost of litigation per case x cases litigated = total cost of litigation

C_8X_8 = average cost of lost productivity per day x hospital and rehabilitation stay days = total cost of lost productivity

C_9X_9 = average cost per haemovigilance case x cases = total cost of haemovigilance

Figure 3. Basic cost equation.

accrue if transfusion practices were optimized. In 18 randomly selected Austrian hospitals, transfusion practices varied widely (Table 4). However, by reducing the variability among centers, lowering the average transfusion rate and number of units transfused per patient to that of the lowest five consuming hospitals, the study group identified an opportunity to save 32% to 62% of units transfused.

Acute normovolaemic haemodilution, also a potential cost- and blood-saving alternative, produced 2.5-fold cost savings, using 2.3-fold fewer RBC units in patients undergoing radical retropubic prostatectomy.¹⁴

Table 4. Evaluation of potential blood cost-savings at 18 Austrian hospitals.

Type of Surgery	% of Patients Transfused	Units Transfused per Patient	Potential Savings if Transfusion Practices were Optimized % ^a
THR	16–84	0.3–2.9	59.4
TKR	12–87	0.3–2.8	62.1
CABG	37–71	0.9–2.9	32.1

^a Optimized defined as follows: 1) reduce the average % of patients transfused across all 18 sites to the average % of patients transfused at the five least-consuming sites for total hip replacement (THR) and total knee replacement (TKR) and the two least-consuming sites for coronary artery bypass graft (CABG); 2) reduce the average number of transfused units per patient to the average at the five least-consuming out of 16 sites for THR and TKR and at the two least-consuming out of 6 sites for CABG.

We must acknowledge that interventions to conserve blood are also associated with costs.^{33,51,52,115,116} For example, reinfused RBCs salvaged during joint arthroplasty as compared to allogeneic transfusions would incur an estimated \$5.7 million per QALY.^{33,117} Another strategy commonly employed to reduce transfusion requirements is to administer erythropoietic stimulating agents (ESAs). If anaemia due to surgery¹¹⁸, cancer, or other causes can be anticipated in advance^{119–124}, administration of ESAs may reduce the need for transfusions, but are they worth the extra cost? In one recent study of the cost-effectiveness of epoetin alfa as a transfusion alternative in ICU patients, costs per QALY were between \$34,088 and \$47,149, most sensitive to the risk of nosocomial bacterial infections per RBC unit. In this setting, assuming that RBC transfusions increase infection risk, epoetin alfa was cost-effective.¹²⁵ In another study, eliminating transfusions offset the direct costs of epoetin alfa by 25% to 50%, even without considering the cost-benefit of improving outcomes, and avoiding transfusion risks and the costs for their management.³⁷ A robust and comprehensive evaluation of the cost of blood is essential so that the questions are appropriately posed and outcomes are rigorously assessed. The work undertaken by COBCON 1 and 2 will be of value to economists who conduct such studies.

CONCLUSIONS

Blood, from its acquisition to transfusion through follow-up, is costly to society. Blood is not a resource to be taken for granted, used liberally without accountability, or wasted. Determining the cost of blood from a societal perspective is a complex undertaking that requires consideration of all relevant cost elements, many of which have not been identified previously. At a minimum, we estimate that the cost of blood to society is twofold higher than calculations derived from previous studies. Many elements have yet to be factored in, including the cost of haemovigilance, about which almost nothing is presently known. Adoption of effective strategies to optimize blood usage, reduce variability, and minimize waste would have an enormous impact on lowering overall health-care costs.

SUMMARY

The use of blood and blood products throughout the world's health-care systems contributes substantially to overall health-care costs. Although many prior and worthwhile attempts to estimate the cost of blood have been made, a comprehensive "vein-to-vein" approach that assumes a societal perspective is still needed. Beginning with the costs of donor recruitment, and encompassing all tasks, personnel, and infrastructures associated with blood collection, processing, distribution, pre transfusion preparation, administration, wastage, adverse event handling, and long-term haemovigilance, it is clear that this is an enormous and complex undertaking. Sophisticated knowledge is required about transfusion medicine, clinical outcomes, administrative structures, health-care economics, and blood distribution networks worldwide. The Society for the Advancement of Blood Management has spearheaded an initiative to gather this expertise and to tie all critical cost elements together into one comprehensive and practical model. Once developed, the model will apply to all single-donor blood products, and may be used by academic, private, and multi- or single-center practices to compute costs associated with blood and blood products. The purpose of having such a comprehensive model is severalfold. First, it will serve future research

that seeks to determine the cost-effectiveness of interventions for improving blood safety and optimizing blood utilization. Second, the model will be adaptable to institutions wanting to increase institutional efficiency and reduce costs at each point-of-care. Finally, and perhaps most importantly, it will raise awareness about the economic realities of blood, its impact on individuals, institutions, and society, and encourage practitioners to think more critically about their blood usage patterns.

Practice points

- Blood is a valuable resource and transfusions should be administered only after careful consideration of the risks and benefits
- Monitor and report all transfusion-related adverse events
- Develop and adhere to institutional efforts to conserve blood, eliminate waste, and optimize resources

Research agenda

- Further determinations of the cost of blood products should attempt to utilize an activity-based model to ensure that all relevant cost elements are accounted for
- Analyses of the cost-effectiveness of blood alternatives or interventions aimed at improving blood safety may need to be reperformed once such a model is available
- Haemovigilance systems and their associated costs need to be further explored

ACKNOWLEDGEMENTS

The authors wish to thank the New Jersey Institute for the Advancement of Bloodless Medicine and Surgery and OrthoBiotech for a grant that helped support the preparation of this manuscript and Kathryn J. Lucchesi, PhD, RPh, of DesignWrite, LLC, for providing editorial and writing assistance.

REFERENCES

1. Van Hulst M, De Wolf JT, Staginnus U et al. Pharmaco-economics of blood transfusion safety: review of the available evidence. *Vox Sanguinis* 2002; **83**: 146–155.
2. Jackson BR, Busch MP, Stramer SL & AuBuchon JP. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* 2003; **43**: 721–729.
3. Vamvakas EC. Epidemiology of red blood cell utilization. *Transfusion Medicine Reviews* 1996; **10**: 44–61.
- *4. Goodnough LT, Brecher ME, Kanter MH & AuBuchon JP. Transfusion medicine. First of two parts: blood transfusion. *The New England Journal of Medicine* 1999; **340**: 438–447.
5. Hannon TJ & Gjerde KP. The contemporary economics of transfusions. In Spiess BD, Spence RK & Shander A (eds). *Perioperative transfusion medicine*. 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2006, pp. 13–38.

6. Sloan EM, Pitt E & Klein HG. Safety of the blood supply. *JAMA: The Journal of the American Medical Association* 1995; **274**: 1368–1373.
7. Brooks JP. Reengineering transfusion and cellular therapy processes hospitalwide: ensuring the safe utilization of blood products. *Transfusion* 2005; **45**(supplement): 159S–171S.
8. Blumberg N. Allogeneic transfusion and infection: economic and clinical implications. *Seminars in Hematology* 1997; **34**: 34–40.
9. Williamson LM, Lowe S, Love EM et al. Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *British Medical Journal* 1999; **319**: 16–19.
- *10. Sazama K, DeChristopher PJ, Dodd R et al. Practice parameter for the recognition, management, and prevention of adverse consequences of blood transfusion. *Archives of Pathology & Laboratory Medicine* 2000; **124**: 61–70.
11. Perrotta PL & Snyder EL. Non-infectious complications of transfusion therapy. *Blood Reviews* 2001; **15**: 69–83.
12. Klein HG. Allogeneic transfusion risks in the surgical patient. *American Journal of Surgery* 1995; **170**(supplement 6A): 21S–26S.
13. Dodd RY. Adverse consequences of blood transfusion: quantitative risk estimates. In Nance ST (ed). *Blood supply: risks, perceptions and prospects for the future*. 1st edn. Bethesda, MD: American Association of Blood Banks, 1994, pp. 1–24.
- *14. Kopko PM, Marshall CS, MacKenzie MR et al. Transfusion-related acute lung injury: report of a clinical look-back investigation. *JAMA: The Journal of the American Medical Association* 2002; **287**: 1968–1971.
15. Denton TA, Diamond GA, Matloff JM & Gray RJ. Anemia therapy: individual benefit and societal cost. *Seminars in Oncology* 1994; **21**: 29–35.
16. Barnett A, Cremieux P-Y, Fendrick AM et al. Anemia-related costs for cancer patients. *Journal of Managed Care Medicine* 2002; **6**: 20–28.
17. Levy MM, Abraham E, Zilberberg M & MacIntyre NR. A descriptive evaluation of transfusion practices in patients receiving mechanical ventilation. *Chest* 2005; **27**: 928–935.
18. Rosencher N, Kerckamp HE, Macheras G et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion* 2003; **43**: 459–469.
- *19. Hébert PC, Wells G, Martin C et al. Variation in red cell transfusion practice in the intensive care unit: a multicentre cohort study. *Critical care (London, England)* 1999; **3**: 57–63.
20. Capraro L, Nuutinen L & Myllyla G. Transfusion thresholds in common elective surgical procedures in Finland. *Vox Sanguinis* 2000; **78**: 96–100.
21. Goodnough LT, Soegiarso RW, Birkmeyer JD & Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. *The American Journal of Medicine* 1993; **94**: 509–514.
22. Vincent JL, Baron J-F, Reinhart K et al. Anemia and blood transfusion in critically ill patients. *JAMA: The Journal of the American Medical Association* 2002; **288**: 1499–1507.
23. Dunne JR, Malone D, Tracy JK et al. Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery. *The Journal of Surgical Research* 2002; **102**: 237–244.
24. Taylor RW, O'Brien J, Trotter SJ et al. Red blood cell transfusions and nosocomial infections in critically ill patients. *Critical Care Medicine* 2006; **34**: 2302–2309.
25. Zallen G, Offner PJ, Moore EE et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *American Journal of Surgery* 1999; **178**: 570–572.
26. Moore FA, Moore EE & Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Archives of Surgery* 1997; **132**: 620–624.
27. Corwin HL, Gettinger A, Pearl RG et al. The CRIT study: anemia and blood transfusion in the critically ill – current clinical practice in the United States. *Critical Care Medicine* 2004; **32**: 39–52.
28. Vamvakas EC & Carven JH. Allogeneic blood transfusion, hospital charges, and length of hospitalization: a study of 487 consecutive patients undergoing colorectal cancer resection. *Archives of Pathology & Laboratory Medicine* 1998; **122**: 145–151.
29. Forbes JM, Anderson MD, Anderson GF et al. Blood transfusion costs: a multicenter study. *Transfusion* 1991; **31**: 318–323.
30. Mohandas K & Aledort L. Transfusion requirements, risks, and costs for patients with malignancy. *Transfusion* 1995; **35**: 427–430.

- *31. Cantor SB, Hudson Jr DV, Lichtiger B & Rubenstein EB. Costs of blood transfusion: a process-flow analysis. *Journal of Clinical Oncology* 1998; **16**: 2364–2370.
- *32. Crémieux PY, Barrett B, Anderson K & Slavin MB. Cost of outpatient blood transfusion in cancer patients. *Journal of Clinical Oncology* 2000; **18**: 2755–2761.
33. Jackson BR, Umlas J & AuBuchon JP. The cost-effectiveness of postoperative recovery of RBCs in preventing transfusion-associated virus transmission after joint arthroplasty. *Transfusion* 2000; **40**: 1063–1066.
34. Fergusson D, Hebert PC, Barrington KJ & Shapiro SH. Effectiveness of WBC reduction in neonates: what is the evidence of benefit? *Transfusion* 2002; **42**: 159–165.
35. Wayne AS, Schoenike SE & Pegelow CH. Financial analysis of chronic transfusion for stroke prevention in sickle cell disease. *Blood* 2000; **96**: 2369–2372.
36. Grimm AM, Flaharty KK, Hopkins LE et al. Economics of epoetin therapy. *Clinical Pharmacy* 1989; **8**: 807–810.
37. Sheingold SH, Churchill DN, Muirhead N & Laupacis A. Recombinant human erythropoietin: factors to consider in cost-benefit analysis. *American Journal of Kidney Diseases* 1991; **17**: 86–92.
38. Sheffield R, Sullivan SD, Saltiel E & Nishimura L. Cost comparison of recombinant human erythropoietin and blood transfusion in cancer chemotherapy-induced anemia. *The Annals of Pharmacotherapy* 1997; **31**: 15–22.
39. Kavanagh BD, Fischer BAI, Segreti EM et al. Cost analysis of erythropoietin versus blood transfusions for cervical cancer patients receiving chemoradiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2001; **51**: 435–441.
- *40. Etchason J, Petz L, Keeler E et al. The cost effectiveness of preoperative autologous blood donations. *The New England Journal of Medicine* 1995; **332**: 719–724.
41. Keating EM, Meding JB, Faris PM & Ritter MA. Predictors of transfusion risk in elective knee surgery. *Clinical Orthopaedics* 1998; **357**: 50–59.
- *42. Shander A. The cost of blood: multidisciplinary consensus conference for a standard methodology. *Transfusion Medicine Reviews* 2005; **19**: 66–78.
43. Goodman C, Chan S, Collins P et al. Ensuring blood safety and availability in the US: technological advances, costs, and challenges to payment—final report. *Transfusion* 2003; **43**: 3S–46S.
44. Wallace EL, Churchill WH, Surgenor DM et al. Collection and transfusion of blood and blood components in the United States, 1994. *Transfusion* 1998; **38**: 625–636.
45. Brand A. Immunological aspects of blood transfusions. *Blood Reviews* 2000; **14**: 130–144.
46. Bordin JO, Heddle NM & Blajchman MA. Biologic effects of leukocytes present in transfused cellular blood products. *Blood* 1994; **84**: 1703–1721.
47. Pittman DL. Rationale for universal WBC reduction of blood components? *Transfusion* 2000; **40**: 389.
48. Dzik S, AuBuchon J, Jeffries L et al. Leukocyte reduction of blood components: public policy and new technology. *Transfusion Medicine Reviews* 2000; **14**: 34–52.
- *49. Birkmeyer JD, Goodnough LT, AuBuchon JP et al. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. *Transfusion* 1993; **33**: 544–551.
50. Combs CA, Murphy EL & Laros Jr. RK. Cost-benefit analysis of autologous blood donation in obstetrics. *Obstetrics and Gynecology* 1992; **80**: 621–625.
51. Goodnough LT, Bodner MS & Martin JW. Blood transfusion and blood conservation: cost and utilization issues. *American Journal of Medical Quality* 1994; **9**: 172–183.
52. Duffy G & Tolley K. Cost analysis of autologous blood transfusion, using cell salvage, compared with allogeneic blood transfusion. *Transfusion Medicine (Oxford, England)* 1997; **7**: 189–196.
53. Blumberg N & Heal JM. Immunomodulation by blood transfusion: an evolving scientific and clinical challenge. *The American Journal of Medicine* 1996; **101**: 299–308.
54. Roddie PH, Turner ML & Williamson LM. Leucocyte depletion of blood components. *Blood Reviews* 2000; **14**: 145–156.
55. van de Watering LMG, Hermans J, Houbiers JGA et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. *Circulation* 1998; **97**: 562–568.
56. van de Watering LMG, Brand A, Houbiers JGA et al. Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. *The British Journal of Surgery* 2001; **88**: 267–272.

57. Pruss A, Kalus U, Radtke H et al. Universal leukodepletion of blood components results in a significant reduction of febrile non-hemolytic but not allergic transfusion reactions. *Transfusion and Apheresis Science* 2004; **30**: 41–46.
58. Fisk JM & Snyder EL. Universal pre-storage leukoreduction – a defensible use of hospital resources: the Yale-New Haven Hospital experience. *Developmental Biology* 2005; **120**: 39–44.
59. Houbiers JGA, van de Watering LMG, Verwey PJM et al. Leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994; **344**: 1429–1431.
60. Vamvakas EC. The cost-effectiveness of autologous transfusion revisited: implications of an increased risk of bacterial infection with allogeneic transfusion. *Transfusion* 2000; **40**: 384–386.
61. Thurer RL, Luban NL, AuBuchon JP et al. Universal WBC reduction. *Transfusion* 2000; **40**: 751–752.
62. Jensen LS, Grunnet N, Hanberg-Sorensen F & Jorgensen J. Cost-effectiveness of blood transfusion and white cell reduction in elective colorectal surgery. *Transfusion* 1995; **35**: 719–722.
63. Blumberg N, Heal JM, Kirkley SA et al. Leukodepleted-ABO-identical blood components in the treatment of hematologic malignancies: a cost analysis. *American Journal of Hematology* 1995; **48**: 108–115.
64. Purdy FR, Tweeddale MG & Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Canadian Journal of Anaesthesia* 1997; **44**: 1256–1261.
65. Mynster T, Dybkjaer E, Reimert CM et al. Prestorage leukofiltration of whole blood and SAGM blood prevents extracellular bioactive substance accumulation. *Inflammation Research* 1999; **48**: 363–368.
66. Marik PE & Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA: The Journal of the American Medical Association* 1993; **269**: 3024–3029.
67. Offner PJ, Moore EE, Biffi WL et al. Increased rate of infection associated with transfusion of old blood after severe injury. *Archives of Surgery* 2002; **137**: 711–717.
68. Vamvakas EC & Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. *Transfusion* 1999; **39**: 701–710.
69. National Blood Data Resource Center. Report on blood collection and transfusion in the United States in 1999, <http://www.nbdrc.org/research/bloodsurv.htm>; 2002. accessed August 15.
70. Perkins J, Kaminer L, Kruskall M et al. Should the FDA mandate that autologous units drawn and transfused within a single institution be tested for markers of infectious disease? *Transfusion* 2000; **40**: 752–753.
71. NIH Consensus Development Panel on Infectious Disease Testing for Blood Transfusions. Infectious disease testing for blood transfusions. *JAMA: The Journal of the American Medical Association* 1995; **274**: 1374–1379.
72. Food and Drug Administration. Requirements for testing human blood donors for evidence of infection due to communicable disease agents. Final rule. *Federal Register* 2001; **66**: 31146–31165.
73. Margolis HS, Coleman PJ, Brown RE et al. Prevention of hepatitis B virus transmission by immunization: an economic analysis of current recommendations. *JAMA: The Journal of the American Medical Association* 1995; **274**: 1201–1208.
74. Busch MP & Dodd RY. NAT and blood safety: what is the paradigm? *Transfusion* 2000; **40**: 1157–1160.
75. Reesink HW, Engelfriet CP, Vrieling H et al. Consequences of nucleic acid amplification testing for blood transfusion centres. *Vox Sanguinis* 1998; **74**: 263–270.
76. Legler TJ, Riggert J, Simson G et al. Testing of individual blood donations for HCV RNA reduces the residual risk of transfusion-transmitted HCV infection. *Transfusion* 2000; **40**: 1192–1197.
77. Stramer SL, Caglioti S & Strong DM. NAT of the United States and Canadian blood supply. *Transfusion* 2000; **40**: 1165–1168.
78. AuBuchon JP, Birkmeyer JD & Busch MP. Cost-effectiveness of expanded human immunodeficiency virus-testing protocols for donated blood. *Transfusion* 1997; **37**: 45–51.
79. Jackson BR, AuBuchon JP & Busch MP. Cost-effectiveness of nucleic acid testing for HIV and HCV in donated blood. *Transfusion* 2000; **40**(supplement): 1385 (abstract).
80. Pelletier JP, Transue S & Snyder EL. Pathogen inactivation techniques. *Best Practice & Research. Clinical Haematology* 2006; **19**: 205–242.
81. AuBuchon JP, Pickard CA, Herschel LH et al. Production of pathogen-inactivated RBC concentrates using PEN110 chemistry: a Phase I clinical study. *Transfusion* 2002; **42**: 146–152.
82. Hambleton J, Viele M, Rios J et al. RBCs treated with Helinx™ pathogen inactivation have recovery and half-life comparable to conventional RBCs in a randomized crossover trial. In *Proceedings of the 7th Annual Congress of the European Hematology Association* 2002. Florence, Italy.

- *83. Laupacis A & Fergusson D. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Transfusion Medicine (Oxford, England)* 1998; **8**: 309–317.
84. Titlestad K, Kristensen T, Jorgensen J & Georgsen J. Monitoring transfusion practice - a computerized procedure. *Transfusion Medicine (Oxford, England)* 2002; **12**: 25–34.
85. Jensen NJ & Crosson JT. An automated system for bedside verification of the match between patient identification and blood unit identification. *Transfusion* 1996; **36**: 216–221.
86. Sherwood WC, Bauman ET & Glenn T. The use of computers in the blood bank to reduce transfusion risk. In Nance ST (ed). *Blood supply. Risks, perceptions and prospects for the future*. 1st edn. Bethesda, MD: American Association of Blood Banks, 1994, pp. 25–43.
87. AuBuchon JP & Littenberg B. A cost-effectiveness analysis of the use of a mechanical barrier system to reduce the risk of mistransfusion. *Transfusion* 1996; **36**: 222–226.
88. Sazama K. Current good manufacturing practices for transfusion medicine. *Transfusion Medicine Reviews* 1996; **X**: 286–295.
89. Callum JL, Pinkerton PH, Coovadia AS et al. An evaluation of the process and costs associated with targeted lookbacks for HCV and general notification of transfusion recipients. *Transfusion* 2000; **40**: 1169–1175.
90. McCarthy BD, Wong JB, Munoz A & Sonnenberg FA. Who should be screened for HIV infection? A cost-effectiveness analysis. *Archives of Internal Medicine* 1993; **153**: 1107–1116.
91. Hellinger FJ. The lifetime cost of treating a person with HIV. *JAMA: The Journal of the American Medical Association* 1993; **270**: 474–478.
92. Sonnenberg FA, Gregory P, Yomtovian R et al. The cost-effectiveness of autologous transfusion revisited: implications of an increased risk of bacterial infection with allogeneic transfusion. *Transfusion* 1999; **39**: 808–817.
93. Wong JB, Koff RS, Tine F & Pauker SG. Cost-effectiveness of interferon- α 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Annals of Internal Medicine* 1995; **122**: 664–675.
94. Carson JL, Altman DG, Duff A et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion* 1999; **39**: 694–700.
95. Dickie H, Vedio A, Dundas R et al. Relationship between TISS and ICU cost. *Intensive Care Medicine* 1998; **24**: 1009–1017.
96. Schreiber GB, Busch MP, Kleinman SH & Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *The New England Journal of Medicine* 1996; **334**: 1685–1690.
97. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990; **30**: 583–590.
98. Sazama K. Bacteria in blood for transfusion: a review. *Archives of Pathology & Laboratory Medicine* 1994; **118**: 350–365.
99. Papia G, McLellan BA, El Helou P et al. Infection in hospitalized trauma patients: incidence, risk factors, and complications. *The Journal of Trauma* 1999; **47**: 923–927.
100. Vrieling H & Reesink HW. Transfusion-transmissible infections. *Current Opinion in Hematology* 1998; **5**: 396–405.
101. Fransen E, Maessen J, Dentener M et al. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. *Chest* 1999; **116**: 1233–1239.
102. Claas FHJ, Roelen DL, van Rood JJ & Brand A. Modulation of the alloimmune response by blood transfusions. *Transfusion Clinique et Biologique* 2001; **8**: 315–317.
103. Hull RJ, Bray RA, Hillyer C & Swerlick RA. Transfusion-associated chronic cutaneous graft-versus-host disease. *Journal of the American Academy of Dermatology* 1995; **33**: 327–332.
104. Silliman CC. Transfusion-related acute lung injury. *Transfusion Medicine Reviews* 1999; **13**: 177–186.
105. Hebert PC. Disclosure of adverse events and errors in healthcare: an ethical perspective. *Drug Safety* 2001; **24**: 1095–1104.
106. Liu JW, Su YK, Liu CF & Chen JB. Nosocomial blood-stream infection in patients with end-stage renal disease: excess length of hospital stay, extra cost and attributable mortality. *The Journal of Hospital Infection* 2002; **50**: 224–227.
107. Orsi GB, Di Stefano L & Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. *Infection Control and Hospital Epidemiology* 2002; **23**: 190–197.

108. Letarte J, Longo CJ, Pelletier J et al. Patient characteristics and costs of severe sepsis and septic shock in Quebec. *Journal of Critical Care* 2002; **17**: 39–49.
109. Angus DC, Linde-Zwirble WT, Lidicker J et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine* 2001; **29**: 1303–1310.
110. Sazama K. Legal aspects of transfusion medicine. *MLO: Medical Laboratory Observer* 1994; **26**: 33–40.
111. Sullivan P. Developing an administrative plan for transfusion medicine—a global perspective. *Transfusion* 2005; **45**: 224S–240S.
112. Asadi MJ & Baltz WA. Activity-based costing for clinical paths. An example to improve clinical cost & efficiency. *Journal of the Society for Health Systems* 1996; **5**: 1–7.
113. Shander A, Goodnough LT. Objectives and limitations of bloodless medical care. *Current Opinion in Hematology* 2006; **13**:462–470.
114. Monk TG, Goodnough LT, Birkmeyer JD et al. Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropubic prostatectomy. *Transfusion* 1995; **35**: 559–565.
115. Pereira A. Cost-effectiveness analysis and the selection of blood products. *Current Opinion in Hematology* 2000; **7**: 420–425.
116. Chernow B. Blood conservation in critical care—the evidence accumulates. *Critical Care Medicine* 1993; **21**: 481–482.
117. Goodnough LT, Verbrugge D & Marcus RE. The relationship between hematocrit, blood lost, and blood transfused in total knee replacement. Implications for postoperative blood salvage and reinfusion. *The American Journal of Knee Surgery* 1995; **8**: 83–87.
118. Keating EM & Ritter MA. Transfusion options in total joint arthroplasty. *The Journal of Arthroplasty* 2002; **17**: 125–128.
119. Littlewood TJ, Bajetta E, Nortier JWR et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology* 2001; **19**: 2865–2874.
120. Crawford J, Demetri GD, Gabrilove JL et al. Clinical benefits of epoetin alfa therapy in patients with lung cancer. *Clinical Lung Cancer* 2002; **3**: 180–190.
121. Demetri GD, Kris M, Wade J et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *Journal of Clinical Oncology* 1998; **16**: 3412–3425.
122. Gabrilove JL, Einhorn LH, Livingston RB et al. Once-weekly dosing of epoetin-alfa is similar to three-times-weekly dosing in increasing hemoglobin and quality of life. *Proceedings American Society of Clinical Oncology* 1999; **18**: 574a (abstract 2216).
123. Glaspy J, Degos L, Dicato M & Demetri GD. Comparable efficacy of epoetin alfa for anemic cancer patients receiving platinum- and nonplatinum-based chemotherapy: a retrospective subanalysis of two large, community-based trials. *Oncologist* 2002; **7**: 126–135.
124. Frankenfield DL & Johnson CA. Current management of anemia in adult hemodialysis patients with end-stage renal disease. *American Journal of Health-system Pharmacy* 2002; **59**: 429–435.
125. MacLaren R & Sullivan PW. Cost-effectiveness of recombinant human erythropoietin for reducing red blood cells transfusions in critically ill patients. *Value Health* 2005; **8**: 105–116.