

The Nature of Optimal Transfusion Practice – ‘The Art of Transfusion’

a report by

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Blood products are basic to modern healthcare. However, greatly varying consumption patterns exist even between countries of similar disease spectrum and macroeconomic status.^{1,2} Variations are even greater for the use of plasma products than for the use of erythrocytes.

Globally, the value of blood products consumed amounts to at least €15 billion.³ Such vast resources should be spent on as sound a basis as possible. A general suspicion exists of overuse of blood products in many rich countries, while, in contrast, the majority of people have poor or no access at all to blood products when ill.

Evidence-based medicine may be defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the individual patient.”⁴ This ideal applies to transfusion as well as to all other medical disciplines. However, clinical practice does not depend only on available external evidence,⁴ and the practice of transfusion does not depend only on the actual clinical situation. The French transfusionist Bahman Habibi wrote in 1999:

“Transfusion medicine is a unique human achievement which integrates science, technology, medicine, public health administration and the community as a whole. I am not aware of any similar example of such an achievement in the history of medicine.”⁵

A Norwegian professor of community science, Ole Berg, recently proposed to describe transfusion as a dynamic triangle depicting a continuous interaction between the needs of the patient as judged by the clinician, the safety-seeking of regulators, the

development of technology by profit-seeking industry and properties and interests of the donors (see *Figure 1*). The purpose of this article is to analyse the transfusion triangle from the viewpoint of the transfusionist, who is expected to have high scientific and technical skills, act as an advisor to clinicians as well as political and administrative regulators, interact with the industry and recruit and maintain blood donors. A main purpose of the International Society for Blood Transfusion (ISBT) is to promote research and improve the scientific basis upon which transfusion is undertaken. Science in transfusion implies basic, natural, clinical and socioeconomic science. One of the main goals of the ISBT is to improve transfusion in poor countries with insufficient healthcare systems. For progress to be made in transfusion in such countries, these facts should be duly appreciated.

Clinical Transfusion

The life-saving effect of transfusion is evident in patients in shock from bleeding. Similarly evident are the effects of administration of clotting factors to haemophiliacs and the prophylactic effect of thrombocyte transfusion in bone-marrow-depressed patients. On the other hand, blood products are drugs, and modern drugs are usually introduced only upon extensive clinical testing. This has not been the case for transfusion until recent years.

Blood products are applied clinically for four main indications:

- maintenance of intravascular fluid volume (‘blood volume’) in order to secure blood supply to vital organs – available blood products are:
 - albumin;

1. G Sirchia, A M Giovanetti, D B L McClelland and G N Frachia (1994), Safe and Good Use of Blood in Surgery (SANGUIS), Use of blood products and artificial colloids in 43 European hospitals, Luxembourg: Office for Official Publications of the European Communities.
2. H E Heier, “Production and consumption of blood products in Norway”, J. Nor. Med. Ass., 113 (1) (1993), pp. 18–22 (in Norwegian).
3. H E Heier (2000), Blood and Society, University of Oslo: Centre for Health Administration (in Norwegian).
4. D L Sackett, W M C Rosenberg, J A M Gray, R B Haynes and W S Richardson, “Evidence-based medicine: what it is and what it isn’t”, Br. Med. J., 312 (13 January 1996), pp. 71–2.
5. B Habibi, “Transfusion yesterday: A project for the third millennium?”, Transfusion Today, 41 (1999), pp. 3–4.

- provision of adequate transportation of oxygen from lungs to peripheral tissues – available blood products are:
 - erythrocyte concentrates;
- ensuring adequate haemostasis – available blood products are:
 - whole blood,
 - thrombocyte concentrates,
 - plasma and
 - coagulation factors; and
- modulation of immune response – available blood products are:
 - gammaglobulin for intramuscular injection (specific and non-specific) and
 - gammaglobulin for intravenous injection (non-specific).

There are no indications for transfusion that cannot be included in this list. On the other hand, transfusion is usually not applied for the specific treatment of nosologically defined diseases, but rather to compensate for physiological deficiencies that can occur in a large spectrum of diseases. Thus, the correct approach to clinical transfusion is a physiological one. This article will focus mainly on the treatment of acute bleeding anaemia and on general aspects of the supply and use of blood products in the world today.

Management of Acute Bleeding Anaemia

Available evidence comes from three sources:

- basic physiological considerations;
- operations without transfusion in Jehova’s Witnesses; and
- clinical trials of different transfusion regimens in critically ill patients.

The general principle of normovolemic haemodilution was introduced by Messmer, et al.⁶ In essence, a normovolemic, otherwise healthy individual at rest can increase cardiac output so as to keep total oxygen-carrying capacity unchanged until haematocrit reaches about 25% (haemoglobin concentration = 7–8g/dl) (see Figure 2). Therefore, in acute blood loss, the main priority is to keep the patient normovolemic.

Normovolemia can be maintained by infusion of saline solutions, dextrans or starch solutions or

Figure 1: The Dynamic Transfusion Triangle

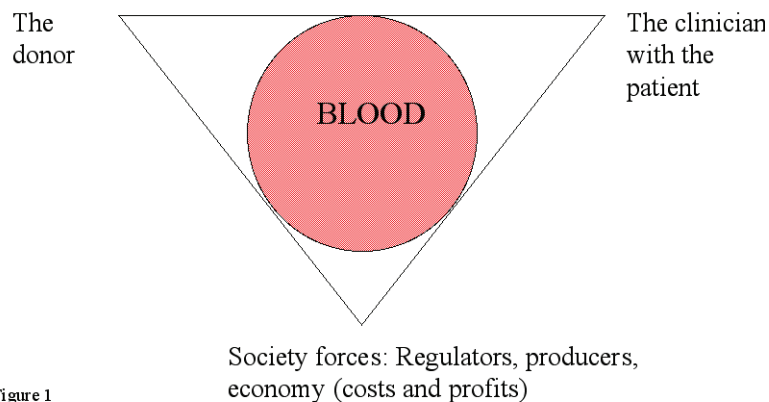


Figure 1

O Berg (1999)

Figure 2: Relative O₂ Transportation Capacity in the Otherwise Healthy, Normovolemic Individual at Rest

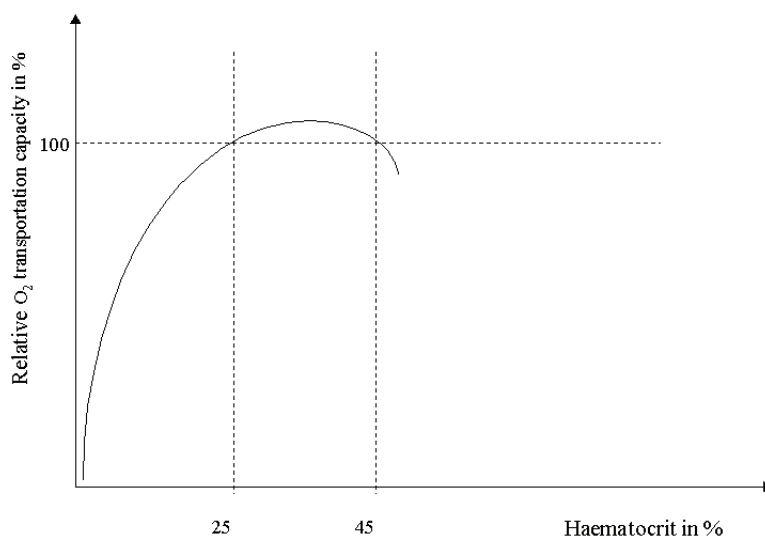


Figure 2

Increase of cardiac output maintains or even increases the capacity until haematocrit reaches about 25%. Modified after Reference 6.

albumin. The global consumption of albumin for transfusion is around 500 tons dry weight, administered usually as 20% concentrates or as 4% to 5% isotonic solutions. Fractionation of albumin from human plasma was developed by Edwin Cohn during World War II as a substitute for labile plasma for the treatment of injured soldiers in shock. The industry of producing albumin became the basis for further refinement of plasma fractionation to yield today’s coagulation factor and gammaglobulin preparations. Great investments were made that needed their profit. However, not until HIV/AIDS appeared were trials conducted to define the optimal use of plasma products. In 1998, a Cochrane group meta-analysis of clinical trials of albumin concluded preliminarily that albumin infusion might be of no beneficial effect or may

6. K Messmer, L Sunder-Plassmann, W P Klövekorn and K Holper, “Circulatory significance of hemodilution: Rheological changes and limitations”, Adv. Microcirc., 4 (1972), pp. 1–77, Karger, Basel.

even have negative effects in critically ill patients with hypoalbuminaemia.⁷ The subject still remains open to debate. In open heart surgery, albumin does not seem superior to artificial colloids and may even be replaced by Ringer's lactate.⁸

In an otherwise healthy, normovolemic patient, there is therefore no physiological need to transfuse erythrocytes until haematocrit reaches values below 25%. Data from operations on Jehova's Witnesses indicate, though, that morbidity and mortality increase if haematocrit is further reduced.⁹ Tolerance to low haematocrit decreases if the patient has cardiovascular or lung disease. All this knowledge is well summarised in the UK guidelines for red cell transfusion.¹⁰

Recent clinical trials indicate that a restrictive attitude to the transfusion of erythrocytes in intensive care patients is better than a liberal strategy.¹¹ This somewhat surprising conclusion has not been fully explained in physiological terms, but stored blood is not, in every respect, equal to the patient's own. In currently used storage media, the oxygen-carrying capacity of haemoglobin is reduced due to loss of 2,3 diphosphoglycerate, and erythrocytes become rigid and less deformable due to loss of adenosine triphosphate (ATP).¹² Furthermore, leucocytes remaining in non-leucocyte-reduced erythrocyte concentrates may modulate the immune response in the patient so as to enhance the frequency of bacterial infections.^{13,14}

It is evident from these considerations that transfusion should be considered a dramatic decision that should rest on the judgement of a clinician with deep insight into physiology and who is continuously evaluating the total situation of the individual patient. Such an attitude should also be borne in mind when transfusing other blood products and in other clinical situations. The conclusion has been

reached without taking into account the small, but real risk of transmitting viral diseases and the frequently forgotten, but very real risk of transfusing incompatible erythrocytes. Haemolytic transfusion reaction, especially to ABH and other carbohydrate antigens, remains a vital risk challenging the logistics of all transfusion systems.^{15,16}

Social Forces – Setting the Goals of Transfusion: Expectations, Safety, Supply, Economy

The ideal transfusion practice is where there is consensus on the clinical goals to be achieved, indications are firm, products are 100% safe and continuously available at the clinician's request, there is no malpractice, economy is adequate and there is a sufficient number of donors. This situation will never occur. Some problems and conflicts deserve to be mentioned.

- There is no worldwide consensus on the goal of treatment for haemophilia. Initially, use was promoted by committed haemophilia doctors, who had a new and highly effective treatment tool, and by profit-seeking fractionation industry, but the goal of treatment was not set. Should one strive for a total compensation of this handicap, applying, for example, extensive prophylactic regimens, or should the patients accept some limitations due to their handicap and receive treatment only when bleeding? Similar countries have developed different strategies and consumption patterns, but attempts to compare clinical results have been insufficient. Although interpretation should be very careful, it is interesting to note that consumption of FVIII has been higher in Denmark and Sweden than in Norway, which lacks a domestic fractionation industry, but has a well-developed national price system (see Table 1).

7. Cochrane Injuries Group Albumin Reviewers, "Human albumin administration in critically ill patients: systematic review of randomised controlled clinical trials", *Br. Med. J.*, 317 (25 July 1998), pp. 235–40.

8. S Tollefsrud, J L Svennevig, H Breivik, U Kongsgard, M Øzer and E Hysing, et al., "Fluid balance and pulmonary functions during and after coronary bypass surgery: Ringer's acetate compared with dextran, polygeline or albumin", *Acta Anaesthesiol. Scand.*, 39 (1995), pp. 671–7.

9. C S Kitchens, "Are transfusions overrated? Surgical outcome of Jehova's witnesses", *Am. J. Med.*, 94 (1993), pp. 117–9.

10. L Williamson, "Transfusion triggers in the UK", *Vox Sang*, 83 (Suppl 1) (2002), pp. 217–9.

11. M A Blajchman and P Hébert, "Red blood cell transfusion strategies", *Transfus. Clin. Biol.*, 8 (2001), pp. 207–10.

12. P L Mollison, C P Engelfriet and M Contreras (1997), *Blood Transfusion in Clinical Medicine*, 10th edition, pp. 289–300, Blackwell Science.

13. R W Taylor, L Manganaro, J O'Brien, S Trottier, N Parkar and C Veremakis, "Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient", *Crit. Care Med.*, 30 (10) (2002), pp. 2,249–54.

14. R J Gazmuri and S A Shakeri, "Blood transfusion and the risk of nosocomial infection: An underreported complication?", *Crit. Care Med.* (Editorial), 30 (10) (2002), pp. 2,389–90.

15. P Rouger, F Noizat-Pirenne and P-Y Le Pennec, "Haemovigilance and transfusion safety in France", *Vox Sang*, 78 (Suppl 2) (2000), pp. 287–9.

16. L Williamson, H Cohen, E Love, H Jones, A Todd and K Soldan, "The serious hazards of transfusion (SHOT) initiative: The UK approach to haemovigilance", *Vox Sang*, 78 (Suppl 2) (2000), pp. 291–5.

Table 1: Increased availability is associated with increased consumption.

Country	FVIII consumption IU/1,000 inhab/year	Whole blood donations/ 1,000 inhab/year	National self-sufficiency for plasma products	Plasm-aphereses/ 1,000 inhab/year	Consumption of erythrocyte conc/1,000 inhab/year	Domestic fractionation industry*	Cost-covering price system for blood products
Denmark	4.3	74	Yes	? (Low)	67	Yes	No
Sweden	4.4	55	Yes	19	49	Yes	Partial
Norway	2.4	43	Yes	1.5	39	No**	Yes

*Based on domestic plasma

** National contract fractionation at plant abroad since 1988

FVIII consumption (equal to self-sufficiency), donation frequencies, consumption of erythrocyte concentrates, presence of domestic fractionation industry and of cost-covering price systems in three Nordic countries before the era of recombinant FVIII (1992).

- Technology can solve many problems, but may also create new ones. Solvent-detergent (S/D) plasma made from pools is even safer against transmission of enveloped viruses such as HIV and hepatitis B and C than thoroughly tested single units of fresh frozen plasma. However, the risk of transmitting non-enveloped viruses to large numbers of recipients may more than outweigh this marginal increase of safety.¹⁷ S/D treatment almost doubles the cost of fresh frozen plasma. Testing for hepatitis C by polymerase chain reaction increases costs of testing by about 40% with only marginal effects on safety and makes the issue of very fresh products difficult or impossible.
- Stringent donor selection criteria are set to prevent the transmission of infectious diseases, but, if too stringent, they may compromise blood supply. Adequate supply is also a safety issue. This dilemma is becoming increasingly evident.¹⁷⁻¹⁹
- Currently, in many industrialised countries, the consumption of gammaglobulin for intravenous use for immunomodulation is increasing significantly for a variety of indications. However, the use of this new and fascinating therapeutic principle should rest on rigorously performed clinical trials. Some are currently in progress, and the results are awaited eagerly. It should not be forgotten that the preparations come from pooled plasma, with the always inherent threat of mass infection should a not inactivated infectious agent occur in a pool.
- The most basic need of all transfusion systems remains ensuring the identity of the patient and the donor. For the safety of transfusion, it is more important to ensure that all patients in a hospital can be identified safely than to introduce, for

example, technically sophisticated, expensive systems for infection testing with only marginal effects on safety. By priority, then, the next basic needs for transfusion of red cells would be:

- properly conducted ABO grouping of donor and patient,
- cross-matching of the patient’s serum against the donor’s erythrocytes,
- anti-HIV 1/2, HBV antigen and anti-HCV testing of donors and
- measurement of haemoglobin before and after transfusion.

Evidence-based transfusion practice should also include the collection of evidence in the individual patient that transfusion was based on sound, clinical judgement and that it produced an acceptable result. Even in advanced transfusion services, such documentation is frequently lacking. The new Blood Directive of the European Union demands systems for haemovigilance to be set up in all Member States. This should be considered a main step forwards for future evidence-based practice of transfusion medicine.

- There is, in general, no linear relationship between resources spent and safety or health profit achieved (see *Figure 3*).²⁰ Rather, investments to meet basic needs give much better pay-off for safety than additional high-cost, technologically interesting equipment and methods.

The Donor

Blood products are of human origin, frequently donated without compensation, and the gift should be treated and used with great respect. Surprisingly few

17. J AuBuchon (2002), “Evolution to the 21st century”, Blood Banking and Transfusion Medicine (Eds C D Hillyer, L E Silberstein, P M Ness and K C Anderson), pp. 3–7, Churchill Livingstone.

18. E Sandborg, “Getting people to give blood”, Vox Sang, 78 (Suppl 2) (2000), pp. 297–301.

19. H E Heier and V Bosnes, “Emerging problems of donor recruitment and maintenance in Oslo, Norway, Abstract P 670 ISBT VII European Congress Paris 15–18 July 2001”, Transfus. Clin. Biol., 8 (Suppl. 1) (2001), p. 238.

20. P Tugwell, C Sithi-Amorn, A O’Connor, J Hatcher-Roberts, Y Bergevin and M Wolfson, “Technology assessment. Old, new and needs-based”, Int. J. Techn. Ass. Health Care, 11 (4) (1995), pp. 650–62.

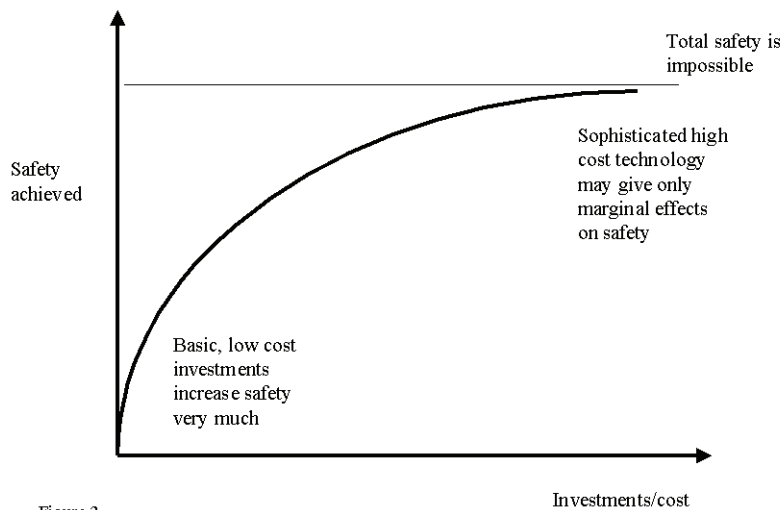
Figure 3: Safety and Health Gain as a Function of Costs in Healthcare

Figure 3

Simplified, but in accordance with Reference 20.

scientific studies have been conducted on motivation factors for blood donors, despite the obvious fact that the whole system of transfusion will collapse if donors do not volunteer. Many cities in the western world are currently faced with increasing troubles in recruiting and maintaining blood donors. Donors become fewer and older,^{19,21} and intensive recruitment campaigns fail to produce lasting results. A recent study of voluntary, non-remunerated donors in Norway²² concluded that established donors are the best recruiters and that selection criteria should be rational and easily understandable for the donors.

Accordingly, making voluntary, non-remunerated blood donation a truly good experience is the best way of maintaining an adequate donor reserve. Selection criteria should be defined and managed at a level that offers the main message of welcoming the donor rather than as being an assessment of whether they fulfil the criteria. Offering oneself as a donor should not be perceived as trying to pass an examination. Furthermore, the transfusion service should be willing to meet the needs of the donors, offering, for example:

- a mobile donation service;
- lunch to donors during working hours; and

- proactive, open and adequate information on any aspect of blood banking.

Unfortunately, current consumption of plasma products in many industrialised countries can only be met and maintained by the use of plasma from remunerated donors. Evidence is clear that remunerated donors are more prone to carrying transmissible diseases than non-remunerated ones.^{23,24} This dilemma applies more than anything to anti-D being used for a prophylactic regimen, which is one of the great triumphs of immunology and is given to more than 100,000 women each year, but also to much of the increasingly used intravenous gammaglobulin preparations. In the author's opinion, the use of remunerated donors can only be justified if the products obtained have been shown conclusively to give better results than alternative treatment procedures.

Conclusion

'The art of transfusion' implies making sure that the patient gets the best therapy possible within the frames defined by biomedical scientific evidence, clinical judgement, technological development, safety, supply and economy. Optimal transfusion practice is no static notion, as it is influenced and modified continuously by forces of a highly variable nature. More evidence by several sciences is urgently needed to improve the basis for defining optimal practice, but there is good reason to promote, in general, a restrictive use of blood products. Globally, the even greater challenge is to provide all fellow human beings with access at least to basic transfusion facilities. This goal remains remote. ■

Additional Information

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21. Finnish Red Cross Blood Transfusion Service (FRCBTS), *Annual Report 2001*, FRBTS, SF-00310 Helsinki 2002.

22. A Misje, "Altruism behind every drop?", *Thesis for Master's degree, Institute of Sociology, University of Bergen, Norway, 2001.*

23. R Beal and W G van Aken, "Gift or good? A contemporary examination of the voluntary and commercial aspects of blood donation", *Vox Sang*, 63 (1992), pp. 1–5.

24. C L van der Poel, E Seifried and W P Schaasberg, "Paying for blood donations, still a risk?", *Vox Sang*, 83 (2002), pp. 285–93.