# Blood management: transfusion medicine comes of age

Blood transfusions happen in more than 10% of all hospital stays that include a procedure. The American Medical Association[1] identified overuse of five medical treatments—blood transfusions, along with cardiac stents, ear tubes, antibiotics, and the induction of birth in pregnant women—and highlighted the danger of unnecessary transfusions. Although blood transfusions are believed to be lifesaving, this assumption has never been shown in a controlled clinical trial; blood transfusions have been described as "unavoidably, unsafe, and inherently dangerous" in the US Blood Shield laws.[2] Thus, perceived benefits relative to the known risks of a blood transfusion are important elements in discussions with patients about informed consent, especially in management of anaemia with alternatives to blood transfusion.[3]

Transfusion-transmitted infections have been a worry, especially in the 1980s with the recognition of transfusion-associated HIV and the risk of transmission of hepatitis C virus.[4] Transmission of known viral agents has decreased and responses to emerging infectious diseases transmitted by blood transfusion have been rapid (figure). Concomitantly, the 2011–12 annual report of transfusion fatalities by the US Food and Drug Administration Center for Biologics Evaluation and Research showed a decrease in all-cause deaths related to transfusion, with only 30 deaths attributable to transfusion reported in the USA in 2011.[5] Between 20x07 and 2011, transfusion-related acute lung injury caused the highest percentage (43%) of reported fatalities, followed by haemolytic transfusion reactions (23%) caused by non-ABO (13%) or ABO (10%) incompatibilities.

Increasing evidence suggests that patients have additional adverse clinical outcomes (ie, increased morbidity and mortality) associated with blood transfusions.[6] The panel lists risks that include not only known transmissible pathogens for infectious disease, transfusion reactions, transfusion-related acute lung injury, errors in blood administration, and circulatory overload; but also potential, as yet undefined, risks such as immunomodulation (eg, perioperative infection or tumour progression), unknown risks (emerging pathogens such as new variant Creutzfeldt-Jakob disease and West Nile virus),[4] and risks associated with duration of blood storage lesions in patients undergoing cardiac surgery.[7] The potential threat of xenotropic murine leukemia virus-related virus (XMRV), for example, required extensive research to determine that its presence in the blood of patients with chronic fatigue syndrome could not be reproducibly confirmed, and that blood donor screening is not warranted.[8]

These considerations have given rise to the specialty of blood management, supported by corresponding initiatives to "promote the appropriate use of blood and blood components, with a goal of minimizing their use". This movement has been motivated by the need to improve blood safety and patient outcomes, preserve the blood inventory, and constrain escalating costs.[9] Patient blood management has been recognised by WHO as a means to "promote the availability of transfusion alternatives".[10] In 2010, blood management was cited as one of the ten key advances in transfusion medicine in the past 50 years.[11]

Awareness of risks, costs, and the effect on blood inventory has led providers to look at institution-based

See **Editorial** page 1789

See **Series** pages 1845, 1855, and 1866

For the **Agency for Healthcare Research and Quality's 2009 Healthcare Cost and Utilization Project report** see http://www.hcup-us.ahrq.gov/reports/factsandfigures/2009/section3_TOC.jsp

For the **Society for the Advancement of Blood Management (SABM)** see http://www.sabm.org

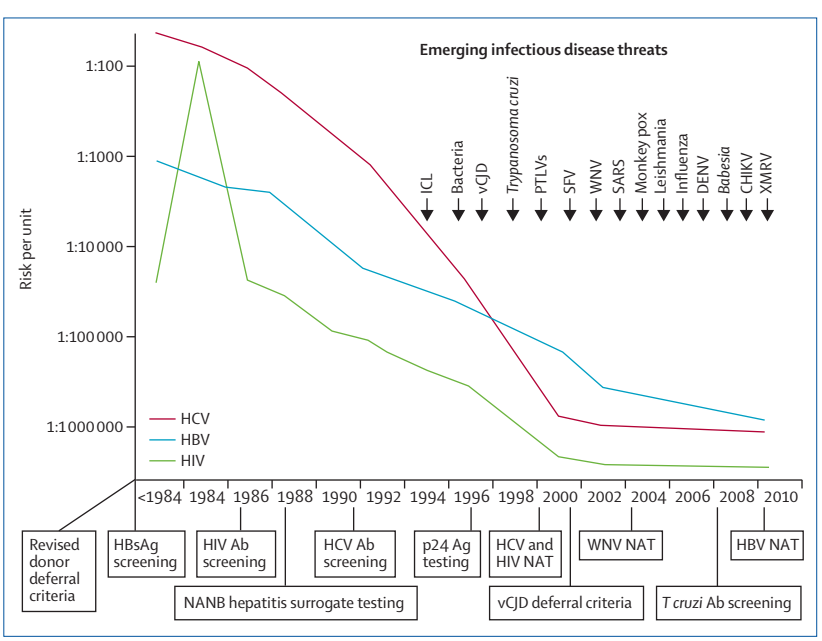



***Figure*: Risks of major transfusion-transmitted viruses related to interventions, and accelerating rate of emerging infectious diseases of concern to blood safety**

Evolution of the risks of transmission by blood transfusion for HIV, hepatitis B virus, and hepatitis C virus. Major interventions to reduce risks are shown below the time line on the X axis. Emerging infectious disease threats in the past 20 years are shown above in the top right quadrant of the figure. HBsAg=hepatitis B surface antigen. Ab=antibody. NANB=non-A, non-B hepatitis. Ag=antigen. HCV=hepatitis C virus. NAT=nucleic acid testing. HBV=hepatitis B virus. ICL=idiopathic CD4 T-lymphocytopenia. vCJD=variant Creutzfeldt-Jakob disease. PTLVs=primate T lymphotropic viruses. SFV=simian foamy virus. WNV=West Nile virus. SARS=severe acute respiratory syndrome. DENV=dengue virus. CHIKV=chikungunya virus. XMRV=xenotropic murine leukaemia virus-related virus. Reproduced with permission from reference 4.

***Panel:* Potential risks of blood transfusion**

1 Infectious agents
- Transfusion-transmitted disease for which donors are tested*
  - Hepatitis B virus (1970 [surface antigen]; 1986–87 [core antibody]; 2009 [nucleic acid])
  - HIV (1985 [antibody]; 1999 [nucleic acid])
  - Hepatitis C virus (1986–87 [alanine aminotransferase]; 1990 [antibody]; 1999 [nucleic acid])
  - Human T-cell lymphotropic virus (1988 [antibody])
  - West Nile virus (2003 [nucleic acid])
  - Bacteria (in platelets only; 2004)
  - *Trypanosoma cruzi* (2007 [antibody])
  - Cytomegalovirus
  - Syphilis
- Transfusion-transmitted disease for which donors are not routinely tested
  - Hepatitis A virus
  - Parvovirus B19
  - Dengue fever virus
  - Malaria
  - *Babesia* spp
  - *Plasmodium* spp
  - *Leishmania* spp
  - *Brucella* spp
  - New variant Creutzfeldt-Jakob disease prions
  - Unknown pathogens

2 Transfusion reactions
3 Alloimmunisation
4 Medical errors (wrong blood to patient because of mislabelled specimen or patient misidentification)
5 Transfusion-associated acute lung injury
6 Transfusion-associated circulatory overload
7 Iron overload
8 Immunomodulation
9 Storage lesions (age of blood)

*The target of the screening assay (antibody, microbial antigen, or microbial nucleic acid) and the year of assay implementation are shown in parentheses. Updated from reference 3.

initiatives in patient blood management, such as the use of guidelines restricting use of transfusion to improve blood use.[12] Patient blood management encompasses an evidence-based medical and surgical approach that is multidisciplinary (ie, including transfusion medicine specialists, surgeons, anaesthesiologists, and critical care specialists) and multiprofessional (ie, including physicians, nurses, pump technologists, and pharmacists). In this approach, preventive strategies are emphasised to identify, assess, and manage anaemia in medical[13] and surgical[14] patients, including use of pharmacological interventions[15] and the avoidance of unnecessary diagnostic teting to minimise iatrogenic blood loss;[16] to optimise homoeostasis[17] and use of point-of-care testing;[18] and to establish clinical practice guidelines for blood transfusions. With recent development of quality–performance indicators for patient blood management by health-care institutions and accreditation organisations,[3] the accompanying Clinical Series in *The Lancet* is appropriate and timely, and looks at the effect of patient blood management on three areas of transfusion medicine: blood utilisation, alternatives to blood, and inventory management of the blood supply.

*Lawrence T Goodnough*
Departments of Pathology and Medicine, Stanford University, Stanford, CA 94305, USA
ltgoodno@stanford.edu

I declare that I have no conflicts of interest.

1 The Joplin Globe. Decline in need for blood leads to staff cuts at center. http://www.joplinglobe.com/local/x2015922821/Decline-in-need-for-blood-leads-to-staff-cuts-at-center (accessed April 10, 2013).
2 Zuck TF. Legal liability for transfusion injury in the acquired immunodeficiency syndrome era. *Arch Pathol Lab Med* 1990; **114:** 309–15.
3 Goodnough LT, Shander A. Patient blood management. *Anesthesiology* 2012; **116:** 1367–76.
4 Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. *Transfusion* 2010; **50:** 2080–99.
5 US Food and Drug Administration Center for Biologics Evaluation and Research. Fatalities reported to FDA following blood collection and transfusion. Annual summary for fiscal year 2011. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM300764.pdf (accessed Jan 8, 2013).
6 Pattakos G, Koch CG, Brizzio ME, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. *Arch Intern Med* 2012; **172:** 1154–60.
7 Wang D, Sun J, Solomon SB, Klein HG, Natanson C. Transfusion of older stored blood and risk of death: a meta-analysis. *Transfusion* 2012; **52:** 1184–95.
8 Simmons G, Glynn SA, Komaroff AL, et al, for the Blood XMRV Scientific Research Working Group (SRWG). Failure to confirm XMRV/MLVs in the blood of patients with chronic fatigue syndrome: a multi-laboratory study. *Science* 2011; **334:** 814–17.
9 Murphy WG. Of mad cows and bolted horses: the economics of blood safety. *Transfusion* 2012; **52:** 2278–81.
10 World Health Organization. 63rd World Health Assembly. Availability, safety and quality of blood products. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf (accessed April 10, 2013).
11 McCullough J. Innovation in transfusion medicine and blood banking: documenting the record in 50 years of TRANSFUSION. *Transfusion* 2010; **50:** 2542–46.
12 The New York Times. Approaching Illness as a Team. Dec 24, 2012. http://www.nytimes.com/2012/12/25/opinion/approaching-illness-as-a-team-at-the-cleveland-clinic.html (accessed April 10, 2013).
13 Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010; **116:** 4754–61.
14 Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth* 2011; **106:** 13–22.
15 Goodnough LT, Shander A. Special article: current status of pharmacologic therapies in patient blood management. *Anesth Analg* 2013; **116:** 15–34.
16 Salisbury AC, Reid KJ, Alexander KP, et al. Diagnostic blood loss from phlebotomy and hospital-acquired anemia during acute myocardial infarction. *Arch Intern Med* 2011; **171:** 1646–53.
17 Goodnough LT, Shander A. How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood* 2011; **117:** 6091–99.
18 Despotis GJ, Joist JH, Goodnough LT. Monitoring of hemostasis in cardiac surgical patients: impact of point-of-care testing on blood loss and transfusion outcomes. *Clin Chem* 1997; **43:** 1684–96.

# Blood: a precious resource

In *The Lancet* today is a Series of three reports on blood transfusion, which present the concepts, alternatives, and challenges. One notable challenge related to transfusion is its overuse, since there are many associated risks (eg, infection). The first report in the Series points out that the identification of non-A non-B hepatitis as one of the most common morbid complications of patients undergoing cardiac bypass, and the advent of HIV, changed the perception that donations from apparently healthy donors were safe. This backdrop of infection has driven the need to explore refinements to blood transfusion and alternative interventions. One such refinement was a reassessment of haemoglobin concentrations needed to prompt transfusion, based on the recognition that physiological compensatory mechanisms meant that moderate anaemia was associated with few symptoms.

The second report in the Series explores alternatives to blood transfusion through more effective management of patients. More conservative approaches to blood transfusion have been shown to reduce hospital mortality and postoperative infections. A patient-centred approach is presented in the second report that attempts to minimise blood transfusion. However, in countries that can afford it, pressure on management strategies can be reduced by finding alternatives to traditional methods of transfusion, such as blood derived from stem-cell sources, which circumvents infectious and immunological risks.

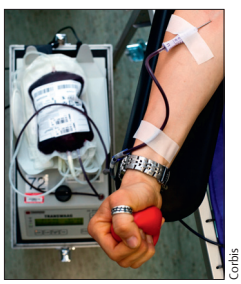
Beyond infection, blood transfusion can present more direct risks. Transfusion-related acute lung injury (TRALI) is considered the most common cause of mortality and morbidity attributable to transfusion; between 2007 and 2011 TRALI caused the greatest number of reported fatalities associated with this procedure in the USA (43%). However, deaths due to TRALI have been reduced by measures to decrease the procurement of plasma and platelets from female donors. For example, women who have been pregnant cannot donate apheresis platelets in Canada, and in the UK donors of fresh frozen plasma and platelets are either male or are negative for HLA antibodies. The third report in the Series expands on the principle of streaming donors. Beyond the streaming of donors purely on safety grounds, streaming on the basis of donor sex can also affect the storage quality of red blood cells. This process has implications for the management of blood and blood products.

Management of blood in low-income and middle-income countries is compounded by additional factors such as the availability of personnel, premises, transport, and power. These complications can make it difficult to ensure the provision of safe and effective blood products. Owing to the difficulties in complying with generally accepted international standards, which include appropriate freezing and cold storage conditions, the ability to trace donors, and testing for viral infections, facilities in these countries must often discard enormous volumes of recovered plasma.

A proposed initiative, endorsed by the WHO Blood Regulators Network, to tackle issues of safety, availability, quality, and accessibility of blood products in low-income and middle-income countries, is the addition of whole blood and red blood cells to the WHO Model Lists of Essential Medicines (EML). This addition is important since governments often consult the EML to guide decisions on resource allocation and spending. So the anticipation is that adding blood to the EML will encourage relevant investment, which should also benefit the development of voluntary unpaid donation by improving standards from donor to recipient.

On June 14, the importance of blood transfusion will be once again highlighted on World Blood Donor Day. In part, the celebration is to "thank voluntary unpaid blood donors for their life-saving gifts of blood". WHO's goal is for all countries to obtain all their blood supplies from voluntary unpaid donors by 2020, since regular donations from this group is the only way to assure an adequate supply—this is only the case in 62 countries so far.

Overuse of transfusion can magnify associated risks, but in places where it is scarce the lack of this intervention only adds to these risks. Although high-income countries should show restraint and innovation in their application of blood transfusion, the recognition of blood as an essential medicine is commendable; the hope is that this will increase the quality and availability of blood products in low-income and middle-income countries. One way to support these measures is to join the celebration of the altruism of voluntary unpaid donors, as described so eloquently in *The Gift Relationship* by Richard Titmuss, and encourage more donors in countries that are not yet self-sufficient for blood products. ■ *The Lancet*



Corbis

See **Comment** page 1791

See **Series** pages 1845, 1855, and 1866

For more on **World Blood Donor Day** see http://www.who.int/campaigns/world-blood-donor-day/2013/en/index.html

For more on **access to blood products in low-income and middle-income countries** see *WHO Drug Info* 2013; **27:** 3–5

# Blood Transfusion 1

# Concepts of blood transfusion in adults

*Lawrence T Goodnough, Jerrold H Levy, Michael F Murphy*

**Recent progress has been made in the identification and implementation of best transfusion practices on the basis of evidence-based clinical trials, published clinical practice guidelines, and process improvements for blood use and clinical patient outcomes. However, substantial variability persists in transfusion outcomes for patients in some clinical settings—eg, patients undergoing cardiothoracic surgery. This variability could be the result of insufficient understanding of published guidelines; different recommendations of medical societies, including the specification of a haemoglobin concentration threshold to use as a transfusion trigger; the value of haemoglobin as a surrogate indicator for transfusion benefit, even though only changes in concentration and not absolute red cell mass of haemoglobin can be identified; and disagreement about the validity of the level 1 evidence for clinical practice guidelines. Nevertheless, institutional experience and national databases suggest that a restrictive blood transfusion approach is being increasingly implemented as best practice.**

## Introduction

Every year, 24 million blood components are transfused in the USA and 3 million in the UK, and transfusions happen in more than 10% of all hospital stays that include a procedure.[1] Of the 39 million hospital discharges in the USA, 5·8% (2·3 million) are associated with blood transfusion.[2] Although blood transfusions are believed to be lifesaving, this hypothesis has never been proven in a prospective controlled clinical trial. Thus, the relative benefit–risk ratio of a blood transfusion is an important bedside discussion for patients' informed consent.[3]

The use of blood has been affected by inherent risks,[4] costs,[5] and inventory constraints.[6] The annual reports of transfusion fatalities by the Serious Hazards of Transfusion (SHOT) scheme in the UK and the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research[7] in the USA show that transfusion-related deaths seem to be falling.[8] In 2011, 69 fatalities among transfusion recipients were reported in the USA and eight in the UK, of which 30 (43%) in the USA and two (25%) in the UK were definitely attributed to transfusion. Since the establishment of the French haemovigilance network in 1994[9] and SHOT in the UK in 1996, transfusion-related acute lung injury (TRALI) has been the most common cause of mortality and morbidity associated with transfusion. Between 2007 and 2011 in the USA, TRALI caused the highest number of reported fatalities (43%), followed by haemolytic transfusion reactions (23%) attributable to non-ABO blood group (13%) or ABO (10%) incompatibilities.[8] The number of deaths related to TRALI has decreased, attributable to initiatives reducing procurement of plasma and platelets from female donors. In view of the known risks and potential for unknown risks of blood in relation to the poorly quantifiable benefit of blood transfusions, the safest blood transfusion is the one not given.[10–12]

Awareness of the risks, costs, and effect on blood inventory has stimulated much interest in both institution-based and national Patient Blood Management initiatives—eg, the National Blood Transfusion Committee in England and AABB Patient Blood Management in the USA.[3,13] These initiatives have led to an increased focus on evidence-based transfusion practices, minimisation of blood loss, and optimisation of patient red blood cell mass, which can each lead to improved patient outcomes. However, the decision to transfuse a patient is not always straightforward. No well-defined clinical criteria are available to show the ideal moment to start transfusion treatment,[14] and the haemoglobin concentration alone poorly shows acute changes in either red blood cell mass (defined as anaemia) or plasma volumes. No one numerical laboratory value can serve as an absolute indicator of the need for transfusion[15] without the context of clinical or patient variables such as risk factors, comorbidities, vital signs, and the rate of anaemia onset (acute *vs* chronic).[16]

### Search strategy and selection criteria

We assessed recent progress to provide a better understanding of best transfusion practices on the basis of evidence-based clinical trials, published clinical practice guidelines, and emerging pathways for improving blood use and clinical patient outcomes. We searched the Cochrane Library, Medline, and Embase for articles published between Jan 1, 2008, and Dec 31, 2012. We used the search terms "blood", "red blood cells", "plasma", and "platelets" in combination with the terms "clinical practice", "transfusion trigger", or "guidelines and recommendations". We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this article has room for. Our reference list was modified on the basis of comments from peer reviewers. Further information on blood transfusions in specific clinical settings such as stem cell and organ transplantation are available from cited references.

*Lancet* 2013; 381: 1845–54

See **Editorial** page 1789

See **Comment** page 1791

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

**Departments of Pathology and Medicine, Stanford University, Stanford, CA, USA** (Prof L T Goodnough MD); **Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA** (Prof J H Levy MD); **and NHS Blood and Transplant, Oxford University Hospitals and University of Oxford, Oxford, UK** (Prof M F Murphy FRCP)

Correspondence to:
Prof Lawrence T Goodnough, Transfusion Service, Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94305-5626, USA
**ltgoodno@stanford.edu**

For more on **Patient Blood Management by the National Blood Transfusion Committee for England** see http://www.transfusionguidelines.org.uk/Index.aspx?Publication=NTC&Section=27&pageid=7728

For more on **AABB Patient Blood Management** see http://www.aabb.org/resources/bct/pbm/pages/default.aspx

For the **Serious Hazards of Transfusion (SHOT) scheme Annual SHOT Report 2011** see www.shotuk.org

## Red blood cell transfusions

### Reassessment of the transfusion trigger

Moderate anaemia has few associated symptoms because of substantial compensatory mechanisms that preserve oxygen transport in the setting of a reduced concentration of haemoglobin. Important physiological compensatory mechanisms are increased blood flow caused by decreased blood viscosity, increased oxygen unloading to tissues because of increased concentration of red cell diphosphoglycerate, maintenance of blood volume attributable to increased plasma volume, and redistribution of blood flow.[16] Symptomatic manifestations arise only when the concentration of haemoglobin is less than two-thirds of normal (ie, <90–100 g/L) because basal cardiac output increases in patients with anaemia and is manifested clinically by fatigue, dyspnoea, and tachycardia (figure 1, appendix).[18] To treat these signs and symptoms, the historical practice was to correct moderate anaemia with red blood cell transfusions or to transfuse blood prophylactically, as in one report that stated "when the concentration of haemoglobin is less than 8–10 g/dL, it is wise to give a blood transfusion before operation".[19]

See Online for appendix

The recognition that transmission of non-A and non-B hepatitis was one of the most morbid complications for patients undergoing cardiac bypass surgery programmes, along with the advent of HIV transmission by blood transfusion[11] led to the realisation that rather than react to the cardiovascular compensatory response to anaemia with blood transfusion treatment, a more appropriate response, in patients who were otherwise stable and not at risk for cardiovascular events, would be to treat patients with fluids to expand intravascular volume and allow the compensatory cardiovascular response to preserve oxygen transport.[20] In resting conditions, oxygen consumption uses only 25% of the oxygen delivered to tissues. Additionally, studies show that no clinically significant difference exists in oxygen delivery between haemoglobin concentrations ranging from 100–60 g/L, mainly because reduced blood viscosity helps to increase blood flow to tissues.[18]

This re-adjustment of the transfusion trigger from a haemoglobin concentration of 100 g/L to a lower threshold[20] was accompanied by the realisation that in populations such as Jehovah's Witness patients who decline blood transfusions because of religious beliefs, postoperative morbidity, and mortality are not recorded until the haemoglobin concentration is very low.[21] Risk only increases for each gram decrement postoperatively when the haemoglobin concentration was less than 70 g/L.[22] This observation was based on the relation between oxygen consumption and oxygen delivery, in which data from Jehovah's Witness patients suggest that the critical rate of haemodilution, defined as the point at which oxygen consumption ($VO_2$) starts to decrease because insufficient oxygen delivery ($DO_2$) is achieved at a haemoglobin concentration of roughly 40 g/L.[23]

Postoperative mortality is significantly increased in patients with cardiovascular disease compared with patients without cardiovascular disease (figure 1).[17] Therefore, the transfusion trigger should be different for patients with cardiovascular disease and patients without cardiovascular disease. A post-hoc analysis of one study[24] was accompanied by an editorial observing that "survival tended to decrease for patients with pre-existing heart disease in the restrictive transfusion strategy group, suggesting that critically ill patients with heart and vascular disease may benefit from higher Hb".[25] This assessment supported a previously published set of clinical practice guidelines that concluded "the presence of coronary artery disease likely constitutes an important factor in determining a patient's tolerance to low Hb".[26] Perioperative myocardial ischaemic episodes are related to haematocrit concentrations less than 28% in patients undergoing radical prostatectomy.[27] A retrospective, observational analysis of Center for Medicare Services (CMS) data for 79 000 elderly patients (>65 years) hospitalised with acute myocardial infarction in the USA found that blood transfusion in patients whose admission haematocrit values were less than 33% were associated with substantially decreased mortality rates.[28] Therefore, a more aggressive use of blood transfusion in the management of anaemia in elderly patients might be warranted.[29] Appreciation of the relative balance between benefits and risks of blood transfusion has led to several randomised controlled clinical trials to better define a haemoglobin concentration as a transfusion trigger.

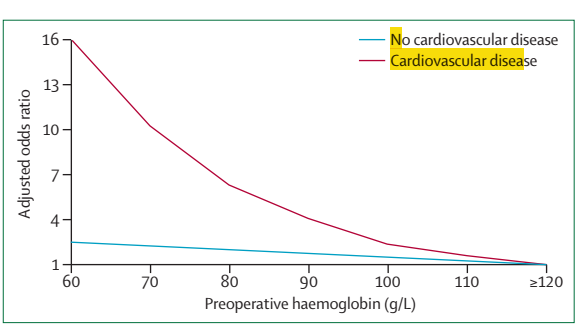



***Figure 1:*** **Adjusted odds ratio for mortality by cardiovascular disease and preoperative haemoglobin**
Reproduced from Carson and colleagues,[17] by permission of Elsevier.

### Clinical trials

Only a few randomised controlled trials have provided level 1 evidence for blood-transfusion practices. A systematic review of published work up to 2000 identified ten trials.[30] The investigators concluded that the evidence supported the use of restrictive transfusion triggers in patients without serious cardiac disease. One report[31] includes study of cardiac surgery at Texas Heart Institute, Houston, TX, USA; patients were randomly assigned by medical record number. Study patients received blood transfusions postoperatively for haemoglobin concentrations lower than 80 g/L and were compared with a control group who had blood transfusions for less than

90 g/L. This study found that a low threshold of 80 g/L did not adversely affect patient outcomes, and the percentage of patients transfused (64% *vs* 60%, respectively) did not differ between the cohorts. Additionally, no difference was seen between the postoperative concentrations of haemoglobin, partly because of the narrow targeted difference by study design, and because of off-protocol transfusions in 38% of the study group and 18% of the control group.

A 2011 Cochrane systematic review[32] of prospective randomised trials compared high versus low haemoglobin concentration thresholds of 19 trials including 6264 patients. The investigators discovered that low haemoglobin thresholds were well tolerated, red blood cell transfusions were reduced by 34% (95% CI 24–45%) in patients randomly assigned to the low haemoglobin cohorts, and the number of red blood cell transfusions was reduced by 1·2 units (0·5–1·8) in the low haemoglobin cohorts. Tables 1 and 2 show the largest and most influential level I studies of red blood cell[33–36] and platelet[37–40] treatment. For red blood cell treatment, four prospective randomised trials of patients in intensive care,[33] patients undergoing cardiothoracic surgery,[34] patients undergoing repair of hip fracture,[35] and patients with acute upper gastrointestinal haemorrhage[36] have each studied whether such patients can tolerate a restrictive transfusion strategy with the threshold for red blood cell transfusion set at a haemoglobin concentration of 70 g/L or 80 g/L. These trials found clinical outcomes were similar to patients transfused to a haemoglobin concentration of more than 90–100 g/L. The Transfusion Requirements in Critical Care (TRICC) trial[33] showed that patients in intensive care could tolerate a restrictive transfusion strategy (haemoglobin concentration range 70–90 g/L, mean 82 g/L) and patients transfused more liberally (haemoglobin concentration range 100–120 g/L, mean 105 g/L), with no differences in 30-day mortality rates. In contrast, a retrospective study of 2393 patients[41] consecutively admitted to the intensive care unit found that an admission haematocrit of less than 25%, in the absence of transfusion, was associated with long-term mortality. Therefore, haematocrit levels below which the transfusion risk to benefit imbalance reverses might exist.

The TRACS trial[34] (NCT01021631) was a large study done at Heart Institute of the University of São Paulo, São Paulo, Brazil of patients randomly assigned to postoperatively receive either restrictive (haematocrit >24%) or liberal (haematocrit >30%) red blood cell transfusions. 30-day all-cause mortality was not different between the two cohorts (10% in patients receiving restrictive transfusions *vs* 11% in patients receiving liberal restrictive transfusions). The FOCUS trial (NCT00071032) found that elderly (mean >80 years of age) high-risk (cofactors for cardiovascular disease) patients who underwent repair of hip fracture surgery, tolerated a haemoglobin trigger without red blood cell transfusions postoperatively to as low as 80 g/L (or higher with transfusions, if symptomatic).[35] In 2013, a prospective study[36] done at Hospital de la Santa Creu i Sant Pau, Barcelona, Spain of patients with upper gastrointestinal bleeding showed that patients randomly

| | Hb concentration threshold (g/L) | Patients transfused | Deviation from transfusion protocol | Mean Hb concentration at transfusion (g/L) | Participation of eligible patients |
|---|---|---|---|---|---|
| Intensive care[33] | 70 *vs* 100 | 67% *vs* 99% | 1·4% *vs* 4·3% | 85 (SD 7)* *vs* 107 (SD 7)* | 41% |
| Cardiothoracic surgery[34] | 80 *vs* 100 | 47% *vs* 78% | 1·6% *vs* 0·0% | 91 (90–92) *vs* 105 (104–106) | 75% |
| Repair of hip fracture[35] | 80 *vs* 100 | 41% *vs* 97% | 9·0% *vs* 5·6% | 79 (SD 6) *vs* 92 (SD 5) | 56% |
| Acute upper gastrointestinal bleeding[36] | 70 *vs* 90 | 49% *vs* 86% | 9·0% *vs* 3·0% | 73 (SD 14) *vs* 80 (SD 15) | 93% |

Hb=haemoglobin. *Average daily Hb. †Different grading systems were used for documenting bleeding.

***Table 1:*** **Key clinical trials of red blood cell transfusions**

| | Comparisons | Patients randomly assigned | Patients transfused off protocol | Median platelet count at transfusion (×10⁹/L) (range) | Patients with grade 2 or greater bleeding† |
|---|---|---|---|---|---|
| Trigger for prophylactic platelet transfusion[37] | Platelet count of 10×10⁹/L *vs* 20×10⁹/L | 135 *vs* 120 | 5·4% *vs* 2·0% | 9 (1–89) *vs* 14 (0–64) | 21·5% *vs* 20·0% |
| Platelet dose[38] | Low dose *vs* medium dose *vs* high dose | 417 *vs* 423 *vs* 432 | 21·0% *vs* 8·0% *vs* 14·0% | 9 (7–16) *vs* 9 (7–19) *vs* 9 (7–12) | 71·0% *vs* 69·0% *vs* 70·0% |
| Prophylactic *vs* therapeutic transfusion[39] | Prophylactic *vs* therapeutic | 197 *vs* 194 | 11·0% *vs* 22·0% | .. | 19·0% *vs* 42·0% |
| Prophylactic *vs* therapeutic transfusion[40] | Prophylactic *vs* therapeutic | 299 *vs* 301 | 23·0% *vs* 14·0% | .. | 43·0% *vs* 50·0% |

Hb=haemoglobin. *Average daily Hb. †Different grading systems were used for documenting bleeding.

***Table 2:*** **Key clinical trials of platelet transfusions**

assigned to a restrictive (haemoglobin concentration <70 g/L versus a liberal (haemoglobin concentration <90 g/L haemoglobin threshold for blood transfusions, had substantially improved outcomes, including mortality at 45 days and rates of rebleeding.

An important limitation of prospectively randomised clinical trials is that patients who are both eligible and who agree to participate in the study might not be representative of all patients in these clinical settings. Only 41% of patients eligible for the TRICC trial[33] and 56% of patients eligible for the FOCUS trial[35] were actually enrolled in the studies, which raised concerns about selection bias; did the treating physicians accurately predict which patients would survive the study, and not enrol the others, thereby ensuring that no differences in survival outcomes would be recorded between treatment groups? Another limitation is the interpretation of the transfusion trigger in these studies. The mean pre-transfusion haemoglobin concentration for patients in the restrictive red cell transfusion group of the TRACS trial was 91 g/L (table 1). However, some reviews and clinical practice guidelines (table 3) have interpreted this study to show that a haemoglobin concentration of 70 g/L is appropriate for use as the transfusion trigger in patients in coronary care. Similarly, the mean haemoglobin concentration for patients in the restrictive group of the TRICC trial was 85 g/L; however, this study has been interpreted as showing that a haemoglobin concentration of 70 g/L is appropriate for use as the transfusion trigger in patients in critical care.

| | Recommendations |
|---|---|
| NIH Consensus Conference,[42] 1988 | <70 g/L (acute) |
| American College of Physicians,[43] 1992 | No number |
| American Society of Anesthesiologists,[44] 1996 | <60 g/L (acute) |
| American Society of Anesthesiologists,[45] 2006 | No number |
| Canadian Medical Association,[26] 1997 | No number |
| Canadian Medical Association,[46] 1998 | No number |
| College of American Pathologists,[47] 1998 | 60 g/L (acute) |
| British Committee for Standards in Haematology,[48] 2001 | No number |
| British Committee for Standards in Haematology,[49] 2012 | 70 g/L* |
| Australasian Society of Blood Transfusion,[50] 2001 | 70 g/L |
| Society for Thoracic Surgeons, Society of Cardiovascular Anesthesiology,[51] 2007 | 70 g/L |
| Society for Thoracic Surgeons, Society of Cardiovascular Anesthesiology,[52] 2011 | 80 g/L* |
| American College of Critical Care Medicine, Society of Critical Care Medicine,[53] 2009 | 70 g/L |
| American College of Critical Care Medicine, Society of Critical Care Medicine,[54] 2009 | 70 g/L |
| Society for the Advancement of Blood Management,[55] 2011 | 80 g/L |
| National Blood Authority, Australia,[13] 2012 | No number |
| AABB,[56] 2012 | 70–80 g/L or 80 g/L† |
| Kidney Disease: Improving Global Outcomes,[57] 2012 | No number |
| National Cancer Center Network,[58] 2012 | 70 g/L |

*For patients with acute blood loss. †For patients with symptoms of end-organ ischaemia.

*Table 3:* **Medical society clinical practice guidelines for red blood cell transfusion**

| | Recommendations |
|---|---|
| British Committee for Standards in Haematology,[59] 1992 | $10\times10^9$/L* |
| College of American Pathologists,[60] 1994 | $5\times10^9$/L* |
| Consensus Conference, Royal College of Physicians, Edinburgh,[61] 1998 | $10\times10^9$/L* |
| American Society of Clinical Oncology,[62] 2001 | $10\times10^9$/L* |
| British Committee for Standards in Haematology,[63] 2001 | $10\times10^9$/L* |
| Italian Society of Transfusion Medicine and Imunohaematology,[64] 2009 | $10\times10^9$/L* |

*Consider raised threshold for patients with additional risk factors for bleeding.

*Table 4:* **Medical society clinical practice guidelines for trigger for prophylactic platelet transfusions**

## Clinical practice guidelines

The number of published clinical practice guidelines for red blood cell (table 3),[13,26,42–58] platelet (table 4),[59–64] and plasma (table 5)[26,60,64–68] blood transfusions show the increasing interest and importance of appropriate blood utilisation by professional societies and health-care institutions. The guidelines generally acknowledge the necessity of considering patient covariables or other patient-specific criteria to make transfusion decisions. Published guidelines generally agree that transfusion is not beneficial when the haemoglobin concentration is greater than 100 g/L, but might be beneficial when the haemoglobin concentration is less than 60–70 g/L.[45–47,50–56] The selection of a discrete concentration of haemoglobin as a trigger for transfusion has been controversial. For example, the initial guidelines by the American Society of Anesthesiology (ASA) in 1996[44] identified a haemoglobin concentration of less than 60 g/L as a transfusion trigger for acute blood loss, whereas the updated 2006 ASA guidelines[41] noted that "although multiple trials have assessed transfusion thresholds on patient outcome, the literature is insufficient to define a transfusion trigger in surgical patients with substantial blood loss."[45]

Three guidelines[42,47,49] have specified a haemoglobin threshold for patients who have acute bleeding only, whereas the concept of an empiric haemoglobin concentration as a transfusion trigger has been refuted by several published clinical practice guidelines.[13,26,43,45,48,57] Arbitrary laboratory values are inadequate to define when red blood cell transfusions are appropriate, so each patient should be assessed individually, and management of anaemia should be patient specific.

## Variability in red blood cell transfusion outcomes

The variability in transfusion outcomes in patients such as those undergoing cardiothoracic surgery has persisted since 1991, even after adjustment for patient-related factors such as diabetes and renal insufficiency.[69–71] The most recent analysis of the Society for Thoracic Surgeons (STS) and Society of Cardiac Anesthesiology (SCA) database showed continued variation in blood transfusion outcomes for patients undergoing coronary artery bypass graft surgery (appendix),[72] despite publication by the societies of clinical practice guidelines in 2007.[51] Similar

| | Main indications |
|---|---|
| Consensus Conference, National Institutes of Health,[65] 1984 | Replacement of isolated factor deficiencies, reversal of warfarin effect, massive blood transfusion, treatment of TTP, antithrombin III deficiency, and immunodeficiencies |
| British Committee for Standards in Haematology,[66] 1992 | Replacement of isolated factor deficiencies in which a specific or combined factor concentrate is unavailable, immediate reversal of warfarin effect, acute DIC, and TTP |
| College of American Pathologists,[60] 1994 | History or clinical course of a coagulopathy (inherited or acquired) with active bleeding or before an invasive procedure, massive transfusion, reversal of warfarin effect, antithrombin III deficiency, immunodeficiencies (in rare instances), and TTP |
| Canadian Medical Association Expert Working Group,[26] 1997 | Several acquired coagulation factor deficiencies—eg, vitamin K deficiency, warfarin, liver disease in which active bleeding is present or before an invasive procedure, acute DIC, massive blood transfusion, TTP, replacement of single coagulation factor deficiencies in which desmopressin or appropriate factor concentrates are unavailable |
| British Committee for Standards in Haematology,[67] 2004 | Replacement of one inherited coagulation factor deficiency in which a virus-safe fractionated product is unavailable, several coagulation factor deficiencies (eg, DIC), TTP, reversal of warfarin effect, vitamin K deficiency in the ICU, and massive transfusion |
| Italian Society of Transfusion Medicine and Imunohaematology,[64] 2009 | Correction of congenital or acquired deficiencies of clotting factors (for which there is not a specific concentrate) when the prothrombin time or a partial thromboplastin time is >1·5 (eg, liver disease), warfarin reversal, acute DIC, or massive transfusion, TTP, reconstitution of whole blood for exchange transfusions, and hereditary angioedema in which C1-esterase inhibitor is not available |
| AABB,[68] 2010* | Massive transfusion in patients with trauma and warfarin-related intracranial haemorrhage |

TTP=thrombotic thrombocytopenic purpura. DIC=disseminated intravascular coagulation. ICU=intensive care unit. *Only six questions relating to plasma use in specific scenarios were considered.

***Table 5:*** **Medical society clinical practice guidelines for plasma transfusion**

data are available from a recent audit of practice of blood transfusions in the UK (figure 2, appendix).

Quality indicators have been established for cardiothoracic surgery programmes in the USA,[51] but blood transfusions are not included. A survey[73] of anaesthetists from more than 1000 North American institutions discovered that although more than three-quarters of anaesthetists and two-thirds of surgeons had read the 2007 STS/SCA guidelines[51] on blood transfusion, only 20% reported an institutional discussion and 14% reported an institutional monitoring group. The poor effect of guidelines in this setting has been attributed to insufficient published level 1 evidence for the recommendations, difficulties inherent to interpretation of clinical trials[73,74] (eg, low participation rate for eligible patients, treatment off-protocol, and so on), and the use of haemoglobin concentration as a surrogate indicator for impaired oxygen delivery and oxygen consumption.[75] Other studies have also shown continued variability in transfusion outcomes for patients undergoing non-cardiac surgery.[76,77]

## Blood use

Both the paediatric[78] and adult hospital[3] at Stanford University Medical Center, CA, USA, have reduced blood use by using the computerised physician order entry process for blood transfusions. The haemoglobin concentration threshold for blood transfusions decreased after clinical effectiveness teams introduced physician education and clinical decision support in July, 2010, via best practices alerts and electronic physician order entry. Figure 2 shows a subsequent analysis of trends in blood use at Stanford University Medical Center. Overall blood component transfusions increased from 2006 to 2009; however, after the best practices alerts were implemented in July, 2010, overall blood component transfusions decreased until 2012 (figure 2A). This decreasing trend was even more pronounced after patient discharges were taken into account (figure 2B). This model of best practices alerts and electronic physician order entry can be used with peer-performance review initiatives in departments to satisfy accreditation requirements for institutional peer review of blood transfusions.

Traditional models of retrospective review for blood use have been ineffective in the improvement of transfusion practices.[15,79] The model of concurrent review at time of physician order entry can be extended to include retrospective analyses of outliers within departments or clinical service lines, in which hospital-based quality committees use these data for physician peer-performance review. National data for the use of red blood cell units in the USA suggest an estimated decrease of 3% in both 2009 and 2010, suggesting that how physicians view blood transfusions is changing.[3] This trend is supported by data from the 2007 National Blood Collection and Utilization Survey,[80] which show a progressive annual decrease in the number of patients and the percentage of hospitals that have cancelled elective surgical procedures because of blood inventory constraints. Similar data are available in England; the demand for red blood cell units steadily increased during the 1990s, successively decreased by 1·3%, 5·9%, 4·4%, 3·5%, and 2·5% in the years from 2003–04 to 2007–08 with an increase of 1·8% in 2008–09 and decreases of 0·1%, 1·4%, and 0·2% in the following

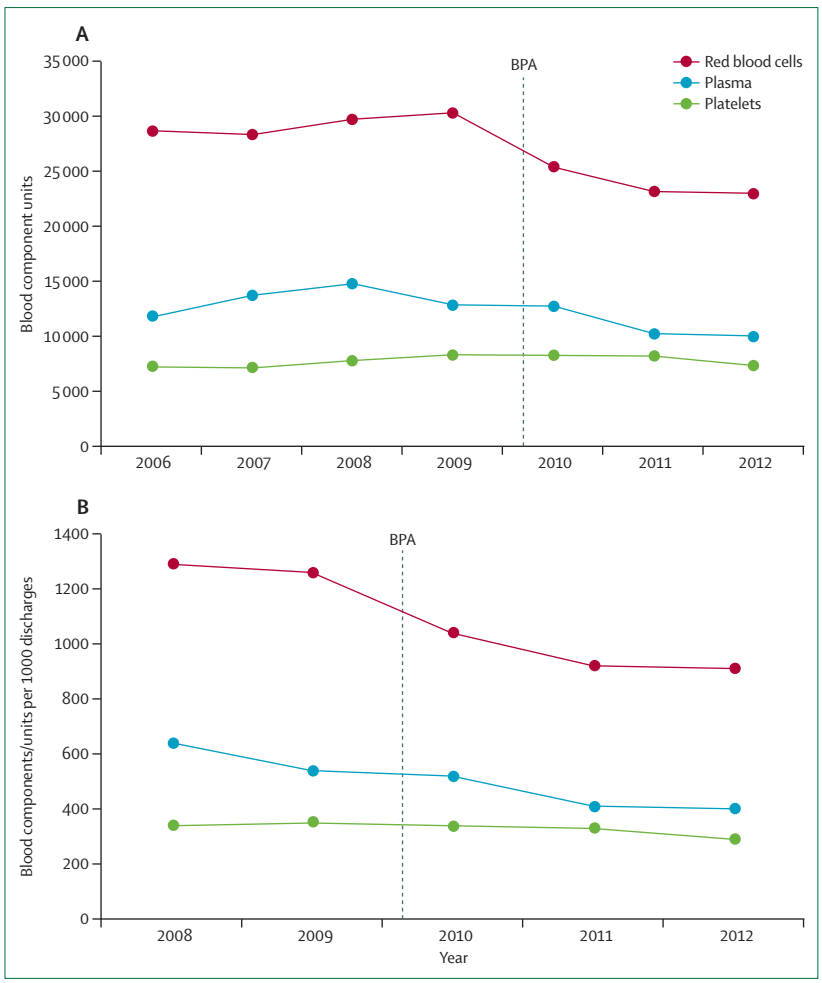



***Figure 2:*** **Trends in blood use at Stanford Hospital and Clinics, USA, 2006–12**
(A) Total red blood cells, plasma, and platelets transfused. Best practices alert (BPA) initiative was initiated July, 2010. Red blood cells, plasma, and platelets transfusions increased between 2006 and 2009, and decreased between 2010 and 2012. (B) Blood components transfused between 2008 and 2012, per 1000 patient discharges at Stanford Hospital and Clinics.

3 years, and a reduction of 2·9% in 2012–13 (Bowden M, NHS Blood and Transplant, personal communication). However, considerable variation remains between hospitals in the reduction of blood use, and national audits of blood components in the UK suggest that overall blood usage could be further reduced without patient safety being compromised.[81]

## Treatment with platelets

Prophylactic platelet transfusions did not become standard practice for haematology, oncology, and stem-cell transplant patients receiving intensive treatment until the 1970s. The use of platelets has become more common since then, and the number of platelet concentrates issued in England rose by 8·3% between April, 2011 and March, 2012.[82] However, although platelet transfusions have improved the management of patients with severe thrombocytopenia, three main areas of controversy remain:[83] what is the optimum prophylactic platelet dose to prevent thrombocytopenic bleeding? Which threshold should be used to trigger the transfusion of prophylactic platelets? Are prophylactic platelet transfusions better than therapeutic platelet transfusions for the prevention of thrombocytopenic bleeding?

Randomised clinical trials have shed light on all three of these areas (table 2[37–40]), and this new evidence, apart from the very recent data on prophylactic versus therapeutic platelet transfusion, has been included in a 2012 systematic review.[83] The platelet count threshold for prophylactic transfusions in patients with haematological cancers has been reduced from 20×10⁹/L to 10×10⁹/L on the basis of trials such as the one done by Rebulla and colleagues,[37] which showed little or no increased bleeding but a substantial reduction in the use of platelet transfusions. In another trial, the dose of platelets had no effect on the incidence of bleeding.[38] The question of the benefit of prophylactic versus therapeutic platelet transfusions has also been studied.[39,40] A recently published trial randomly assigned haematology patients receiving intensive chemotherapy or undergoing haemopoietic stem-cell transplantation to either a no-prophylaxis platelet transfusion strategy or standard prophylaxis with platelet transfusions.[40] The incidence of bleeding was lower in the prophylaxis group than in the no-prophylaxis group (43% *vs* 50%; 90% CI 1·7–5·2 (table 2). Only 59% of patients received a platelet transfusion in the no-prophylaxis group versus 89% in the prophylaxis group. The trial provides evidence for the benefit of prophylactic platelet transfusions in haematology patients in agreement with the results of a previous smaller trial from Germany.[39] All these platelet transfusion trials recorded a high rate of bleeding, which varied according to the methods used to document bleeding, showing the need for new treatment strategies to minimise bleeding in patients with haematological cancers.

National guidelines for platelet transfusions exist in many countries and provide advice on when to transfuse platelets to prevent spontaneous bleeding, before invasive procedures, and when to treat active bleeding (table 4[59–64]). The largest group of patients to receive platelet transfusions are haematology patients, who receive up to 67% of all platelet concentrates.[84] A 2012 survey of platelet transfusions in haematology patients in the UK identified that 34% of prophylactic platelet transfusions were transfused outside the guideline recommendations, and 10% of prophylactic transfusions were given as a double dose.[85] The reasons for this inappropriate use, despite the recent evidence of the appropriate threshold and dose of platelet transfusions, are unclear. Further work is needed to implement the findings of high-quality evidence for good transfusion practice.

## Treatment with plasma

National guidelines exist in many countries and are broadly similar in their recommendations for use of

plasma (table 5[26,60,64–68]). Recommendations for plasma transfusion are: active bleeding before surgery or an invasive procedure in patients with acquired deficiencies of one or more coagulation factors, as shown by abnormalities in the standard coagulation tests; immediate correction of vitamin K deficiency or reversal of warfarin anticoagulant effect in patients with active bleeding; disseminated intravascular coagulation or consumptive coagulopathy with active bleeding; thrombotic thrombocytopenic purpura; and patients with a congenital coagulation factor deficiency for which no alternative treatments are available or appropriate.

Systematic reviews show a paucity of evidence for the effectiveness of plasma; 80 randomised controlled trials of plasma were analysed in two systematic reviews[86,87] with no consistent evidence of benefit for the prophylactic or therapeutic use of plasma in many clinical indications. Studies of plasma treatment have been very restricted: no control groups, only mildly abnormal coagulation test results, absence of or poorly defined clinical endpoints, and inadequate doses of plasma.[86–88] Patients with mild prolonged international normalisation ratios (<1·7) are not at risk of bleeding and do not need plasma transfusion for minor procedures.[89] However, plasma treatment or similar blood components are still widely used in clinical practice in several specialties. The use of these components increased by 3·1% in England between April, 2011, and March, 2012, and by 1·9% in 2012–13 (Bowden M, NHS Blood and Transplant, personal communication). A 2011 UK survey of nearly 5000 patients who had plasma transfusions recorded that 43% of transfusions were given as prophylaxis in the absence of documented bleeding for abnormal coagulation tests or before surgery or other invasive procedures.[90] In 31% of prophylactic transfusions, the international normalisation ratio was 1·5 or less.[90] Changes in coagulation tests after plasma transfusions were generally very small.

Increasing evidence of adverse effects of plasma transfusion compounds raises concerns about the ineffectiveness of the procedure. A 2011 study[91] identified a high incidence (6%) of transfusion-associated circulatory overload in patients in intensive care; the main risk factors for cases of transfusion-associated circulatory overload compared with controls were a more positive fluid balance, higher volumes of plasma transfused, and a faster rate of transfusion. TRALI continues to be the most frequent cause of mortality and morbidity[1] from blood transfusion, although the incidence of injury has decreased with the use of plasma from male donors or female donors with no history of pregnancy.[92,93]

Cryoprecipitate is given to increase the concentration of fibrinogen in patients with acquired hypofibrinogenaemia or to increase the concentration in bleeding patients. The transfusion threshold for fibrinogen concentration is changing, as normal concentrations are increasingly seen as a target for treatment.[94] In countries where cryoprecipitate is not available, fibrinogen concentrates are used.[94]

## Patients with trauma

Haemorrhage is responsible for almost 50% of deaths occurring within 24 h of traumatic injury and for up to 80% of intraoperative trauma mortalities.[95–97] Blood component support before and after control of massive haemorrhage is critical in these scenarios. Traditionally, resuscitation has been initiated with large volumes of crystalloid, accompanied by treatment with red blood cells.[98] Plasma, platelets, and cryoprecipitate are then supplemented on the basis of laboratory values and at the discretion of the anaesthetic and surgical teams. The goal of this strategy is to treat coagulopathy after the patient is stabilised and the acute resuscitation is complete. However, findings from studies suggest that even in cases where clinically apparent coagulopathy attributable to haemorrhage is addressed with early administration of plasma, the amount infused often falls substantially below the amount needed to address the complex coagulopathy related to dilution, consumption, and fibrinolysis.[99] Moreover, administration of large crystalloid volumes is independently associated with increased haemorrhage and decreased survival rates.[100]

An estimated 10% of military patients with trauma and 3–5% of civilian patients with trauma receive massive transfusions (generally defined as >10 units of red blood cells given within 24 h of treatment initiation).[101] This focus on the replenishment of red blood cells does not address a substantial subset of patients who would probably benefit from additional blood component treatment over a shorter interval.[102] Both Moore and colleagues[102] and Holcomb and coworkers[103] showed that patients receiving 10 units of red blood cells in the first 6 h after injury had a higher rate of mortality than did those receiving the same quantity over 24 h. Early identification of this patient population and the adherence to massive transfusion protocols that provide early management of associated coagulopathy have been associated with improved survival.[99]

Because of the need for rapid response, transfusion services have implemented blood-ordering protocols to quickly and efficiently provide sufficient amounts and types of blood products to patients with massive haemorrhage. Many criteria are available to help to assess the effectiveness of different strategies used by transfusion services. Investigation of the effectiveness of these protocols should include several parameters: clinical outcomes (survival, length of hospital stay, multisystem organ failure, infection rate, and so on), postresuscitation laboratory parameters (haemoglobin concentration, prothrombin time, partial thromboplastin time, fibrinogen, and platelet count), and 24-h blood component and crystalloid use.

Observational studies of military and civilian trauma report the benefit of transfusion of whole blood or whole blood equivalents in patients needing massive transfusion with maintained transfusion ratios of 1:1:1 for

units of red blood cells, plasma, and platelets.[104,105] However, other studies have reported increased morbidity such as multiorgan system failure associated with transfusion of plasma products;[106] there seem to be distinct roles for both trauma and for blood transfusion in induction of immune modulation after injury.[105] The use of such formulaic ratios or point-of-care-testing or both are the subject of intense interest to address transfusion medicine support of patients with massive haemorrhage and coagulopathic bleeding.[107]

## Conclusions

Blood transfusions carry risks, and are expensive, and blood supply is scarce. As a result, blood use and transfusion outcomes are under renewed scrutiny by healthcare institutions, regulatory agencies, and accreditation organisations.[3,12,108] Additionally, professional societies are well positioned to incorporate blood transfusion outcomes as quality indicators in their own guidelines and recommendations.[109] Physicians and hospital departments of quality and cost-effectiveness should introduce patient blood management initiatives to improve patient safety and clinical outcomes. Despite recent progress made on the basis of high-quality clinical trials, many uncertainties remain in the identification and implementation of best transfusion practices. The presumed benefits of blood transfusion are being challenged by the findings of recent trials, which show that restrictive transfusion practices are equivalent or better than liberal transfusion practices. Additional data are needed to establish the optimum use of red cell, platelet, and plasma transfusions in different clinical settings—eg, trauma and cardiac surgery. Evidence of an association between decreased use of blood and non-transfusion-based strategies (eg, antifibrinolytic drugs such as tranexamic acid) is increasing, and further trials are needed to show the effectiveness of these strategies in more clinical situations. Finally, more research is needed to overcome clinicians' resistance to change and to find out how best to translate the findings of these clinical trials into clinical practice.

### Contributors

LTG, JHL, and MFM each participated in the research and analysis and preparation of the manuscript.

### Conflicts of interest

LTG, JHL, and MFM have no conflicts of interest.

### Acknowledgments

The authors would like to thank Jason Calcagno for manuscript preparation and administrative support.

### References

1 Healthcare Cost and Utilization Project. HCUP facts and figures 2009. Section 3: inpatient hospital stays by procedure. http://www.hcup-us.ahrq.gov/reports/factsandfigures/2009/section3_TOC.jsp (accessed April 30, 2013).

2 Morton J, Anastassopoulos KP, Patel ST, et al. Frequency and outcomes of blood products transfusion across procedures and clinical conditions warranting inpatient care: an analysis of the 2004 healthcare cost and utilization project nationwide inpatient sample database. *Am J Med Qual* 2010; **25:** 289–96.

3 Goodnough LT, Shander A. Patient blood management. *Anesthesiology* 2012; **116:** 1367–76.

4 Starr D. Blood: an epic history of medicine and commerce. New York: AA Knopf, 1998.

5 Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; **50:** 753–65.

6 Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. Second of two parts-blood conservation. *N Engl J Med* 1999; **340:** 525–33.

7 US Food and Drug Administration Center for Biologics Evaluation and Research. Fatalities reported to FDA following blood collection and transfusion. Annual summary for fiscal year 2011. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM300764.pdf (accessed Aug 20, 2012).

8 Vamvakas EC. Reasons for moving toward a patient-centric paradigm of clinical transfusion medicine practice. *Transfusion* 2013; **53:** 888–901.

9 Carlier M, Vo Mai MP, Fauveau L, Ounnoughene N, Sandid I, Renaudier P. Seventeen years of haemovigilance in France: assessment and outlook. Transfusion clinique and biologique 2011; **18:** 140–50.

10 Pattakos G, Koch CG, Brizzio ME, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. *Arch Intern Med* 2012: **172:** 1154–60.

11 Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts-blood transfusion. *N Engl J Med* 1999; **340:** 438–47.

12 Sack K. The New York Times. 'Bloodless' lung transplants offer hint at surgery's future. Feb 24, 2013. http://www.nytimes.com/2013/02/25/us/bloodless-lung-transplants-for-jehovahs-witnesses.html?pagewanted=all&_r=0 (accessed Feb 28, 2013)

13 National Blood Authority Australia. Patient blood management guidelines. http://www.nba.gov.au/guidelines/review.html (accessed Oct 15, 2012).

14 Bittencourt R, Costa J, Lobo JE, Aguiar FC. Consciously transfusion of blood products. Systematic review of indicative factors for blood components infusion's trigger. *Rev Bras Anestesiol* 2012; **62:** 402–10.

15 Goodnough LT, Audet AM. Utilization review for red cell transfusions. Are we just going through the motions? *Arch Pathol Lab Med* 1996; **120:** 802–03.

16 Goodnough LT, Despotis GJ, Hogue CW Jr, Ferguson TB Jr. On the need for improved transfusion indicators in cardiac surgery. *Ann Thorac Surg* 1995; **60:** 473–80.

17 Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. . *Lancet* 1996; **348:** 1055–60.

18 Finch CA, Lenfant C. Oxygen transport in man. *N Engl J Med* 1972; **286:** 407–15.

19 Adams RC, Lundy JS. Anesthesia in cases of poor surgical risk: some suggestions for decreasing the risk. *Surg Gynecol Obstet* 1942; **74:** 1011–19.

20 Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Crit Care Med* 2006; **34** (suppl 5)**:** 102–08.

21 Spence RK, Costabile JP, Young GS, et al. Is hemoglobin level alone a reliable predictor of outcome in the severely anemic surgical patient? *Am Surg* 1992; **58:** 92–95.

22 Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002; **42:** 812–18.

23 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? *Anesth Analg* 1992; **75:** 818–21.

24 Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; **29:** 227–34.

25 Parrillo JE. Journal supplements, anemia management, and evidence-based critical care medicine. *Crit Care Med* 2001; **29:** 139–40.

26 Expert Working Group. Guidelines for red blood cell and plasma transfusion for adults and children. *Can Med Assoc J* 1997; **156** (suppl 11)**:** 1–24.

27 Hogue CW Jr, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion* 1998; **38:** 924–31.

28 Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; **345:** 1230–36.

29 Goodnough LT, Bach RG. Anemia, transfusion, and mortality. *N Engl J Med* 2001; **345:** 1272–74.

30 Carson JL, Hill S, Carless P, Hebert P, Henry D. Transfusion triggers: a systematic review of the literature. *Transfus Med Rev* 2002; **16:** 187–99.

31 Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion* 1999; **39:** 1070–77.

32 Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012; **4:** CD002042.

33 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. *N Engl J Med* 1999; **340:** 409–17.

34 Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* 2010; **304:** 1559–67.

35 Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365:** 2453–62.

36 Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368:** 11–21.

37 Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. *N Engl J Med* 1997; **337:** 1870–75.

38 Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010; **362:** 600–13.

39 Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* 2012; **380:** 1309–16.

40 Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013; **368:** 1771–80.

41 Mudumbai SC, Cronkite R, Hu KU, et al. Association of admission hematocrit with 6-month and 1-year mortality in intensive care unit patients. *Transfusion* 2011; **51:** 2148–59.

42 Consensus conference. Perioperative red blood cell transfusion. *JAMA* 1988; **260:** 2700–03.

43 Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992; **116:** 393–402.

44 American Society of Anesthesiologists Task Force on Blood Component Therapy. Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; **84:** 732–47.

45 American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. 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.

46 Innes G. Guidelines for red blood cells and plasma transfusion for adults and children: an emergency physician's overview of the 1997 Canadian blood transfusion guidelines. Part 1: red blood cell transfusion. Canadian Medical Association Expert Working Group. *J Emerg Med* 1998; **16:** 129–31.

47 Simon TL, Alverson DC, AuBuchon J, et al. Practice parameter for the use of red blood cell transfusions: developed by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists. *Arch Pathol Lab Med* 1998; **122:** 130–38.

48 Murphy MF, Wallington TB, Kelsey P, et al. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; **113:** 24–31.

49 British Committee for Standards in Haematology (BCSH). Guideline on the administration of blood components. http://www.bcshguidelines.com/documents/BCSH_Blood_Admin_-_addendum_August_2012.pdf (accessed Sept 25, 2012).

50 Australasian Society of Blood Transfusion. Clinical practice guidelines: appropriate use of red blood cells. http://www.nhmrc.health.gov.au (accessed Aug 20, 2012).

51 Ferraris VA, Ferraris SP, Saha SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007; **83** (suppl 5)**:** 27–86.

52 Ferraris VA, Brown JR, Despotis GJ, et al. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011; **91:** 944–82.

53 Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009; **37:** 3124–57.

54 Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *J Trauma* 2009; **67:** 1439–42.

55 Shander A, Fink A, Javidroozi M, et al. Appropriateness of allogeneic red blood cell transfusion: the International Consensus Conference on Transfusion Outcomes. *Transfus Med Rev* 2011; **25:** 232–46.

56 Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline From the AABB*. *Ann Intern Med* 2012; **157:** 49–58.

57 Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; **2:** 311–16.

58 Rodgers GM 3rd, Becker PS, Blinder M, et al. Cancer- and chemotherapy-induced anemia. *J Natl Compr Canc Netw* 2012; **10:** 628–53.

59 Murphy MF, Brozovic B, Murphy W, Ouwehand W, Waters AH. Guidelines for platelet transfusions. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. *Transfus Med* 1992; **2:** 311–18.

60 Cooper ES, Bracey AW, Horvath AE, et al. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.

61 Contreras M. Final statement from the consensus conference on platelet transfusion. *Transfusion* 1998; **38:** 796–97.

62 Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38.

63 Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; **122:** 10–23.

64 Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion of plasma and platelets. *Blood Transfus* 2009; **7:** 132–50.

65 National Heart, Lung, and Blood Institute, Center for Drugs and Biologics of the Food and Drug Administration, Office of Medical Applications of Research. Fresh-frozen plasma. Indications and risks. *JAMA* 1985; **253:** 551–53.

66 Contreras M, Ala FA, Greaves M, et al. Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. *Transfus Med* 1992; **2:** 57–63.

67 O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126:** 11–28.

68 Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion* 2010; **50:** 1227–39.

69 Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology* 1998; **88:** 327–33.

70 Snyder-Ramos SA, Mohnle P, Weng YS, et al. The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion* 2008; **48:** 1284–99.

71 Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. *BMC Med* 2009; **7:** 37.

72 Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010; **304:** 1568–75.

73 Hessel EA 2nd, Levy JH. Guidelines for perioperative blood transfusion and conservation in cardiac surgery: lessons and challenges. *Anesth Analg* 2010; **111:** 1555–59.

74 Likosky DS, FitzGerald DC, Groom RC, et al. Effect of the perioperative blood transfusion and blood conservation in cardiac surgery clinical practice guidelines of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists upon clinical practices. *Anesth Analg* 2010; **111:** 316–23.

75 Goodnough LT, Levy JH. Invited commentary. *Ann Thorac Surg* 2012; **94:** 709.

76 Hutton B, Fergusson D, Tinmouth A, McIntyre L, Kmetic A, Hebert PC. Transfusion rates vary significantly amongst Canadian medical centres. *Can J Anaesth* 2005; **52:** 581–90.

77 Frank SM, Savage WJ, Rothschild JA, et al. Variability in blood and blood component utilization as assessed by an anesthesia information management system. *Anesthesiology* 2012; **117:** 99–106.

78 Adams ES, Longhurst CA, Pageler N, Widen E, Franzon D, Cornfield DN. Computerized physician order entry with decision support decreases blood transfusions in children. *Pediatrics* 2011; **127:** e1112–19.

79 Haspel RL, Uhl L. How do I audit hospital blood product utilization? *Transfusion* 2012; **52:** 227–30.

80 US Department of Health and Human Services. 2007 National Blood Collection and Utilization Survey. http://www.hhs.gov/ash/bloodsafety/2007nbcus_survey.pdf (accessed Aug 21, 2012).

81 Murphy MF, Stanworth SJ, Yazer M. Transfusion practice and safety: current status and possibilities for improvement. *Vox Sang* 2011; **100:** 46–59.

82 Estcourt LJ, Stanworth SJ, Murphy MF. Platelet transfusions for patients with haematological malignancies: who needs them? *Br J Haematol* 2011; **154:** 425–40.

83 Estcourt L, Stanworth S, Doree C, et al. Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev* 2012; **5:** CD004269.

84 Cameron B, Rock G, Olberg B, Neurath D. Evaluation of platelet transfusion triggers in a tertiary-care hospital. *Transfusion* 2007; **47:** 206–11.

85 Estcourt LJ, Birchall J, Lowe D, Grant-Casey J, Rowley M, Murphy MF. Platelet transfusions in haematology patients: are we using them appropriately? *Vox Sang* 2012; **103:** 284–93.

86 Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126:** 139–52.

87 Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion* 2012; **52:** 1673–86.

88 Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005; **45:** 1413–25.

89 Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. *Am J Clin Pathol* 2006; **126:** 133–39.

90 Stanworth SJ, Grant-Casey J, Lowe D, et al. The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children. *Transfusion* 2011; **51:** 62–70.

91 Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion* 2011; **51:** 338–43.

92 Lin Y, Saw CL, Hannach B, Goldman M. Transfusion-related acute lung injury prevention measures and their impact at Canadian Blood Services *Transfusion* 2012; **52:** 567–74.

93 Chapman CE, Stainsby D, Jones H, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009; **49:** 440–52.

94 Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg* 2012; **114:** 261–74.

95 Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 2006; **60**(suppl 6)**:** 3–11.

96 Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg* 1998; **186:** 528–33.

97 Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma* 1995; **38:** 185–93.

98 Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev* 2009; **23:** 231–40.

99 Cotton BA, Dossett LA, Au BK, Nunez TC, Robertson AM, Young PP. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. *J Trauma* 2009; **67:** 1004–12.

100 Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* 2005; **101:** 601–05.

101 Como JJ, Dutton RP, Scalea TM, Edelman BB, Hess JR. Blood transfusion rates in the care of acute trauma. *Transfusion* 2004; **44:** 809–13.

102 Moore FA, Nelson T, McKinley BA, et al. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. *J Trauma* 2008; **64:** 1010–23.

103 Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 2007; **62:** 307–10.

104 Cotton BA, Gunter OL, Isbell J, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma* 2008; **64:** 1177–82.

105 Jackman RP, Utter GH, Muench MO, et al. Distinct roles of trauma and transfusion in induction of immune modulation after injury. *Transfusion* 2012; **52:** 2533–50.

106 Inaba K, Branco BC, Rhee P, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg* 2010; **210:** 957–65.

107 Goodnough LT, Spain DA, Maggio P. Logistics of transfusion support for patients with massive hemorrhage. *Curr Opin Anaesthesiol* 2013; **26:** 208–14.

108 Gammon HM, Waters JH, Watt A, Loeb JM, Donini-Lenhoff A. Developing performance measures for patient blood management. *Transfusion* 2011; **51:** 2500–09.

109 Shander AS, Goodnough LT. Blood transfusion as a quality indicator in cardiac surgery. *JAMA* 2010; **304:** 1610–11.

# Blood Transfusion 2

# Alternatives to blood transfusion

*Donat R Spahn, Lawrence T Goodnough*

**The use of alternatives to allogeneic blood continues to rest on the principles that blood transfusions have inherent risks, associated costs, and affect the blood inventory available for health-care delivery. Increasing evidence exists of a fall in the use of blood because of associated costs and adverse outcomes, and suggests that the challenge for the use of alternatives to blood components will similarly be driven by costs and patient outcomes. Additionally, the risk–benefit profiles of alternatives to blood transfusion such as autologous blood procurement, erythropoiesis-stimulating agents, and haemostatic agents are under investigation. Nevertheless, the inherent risks of blood, along with the continued rise in blood costs are likely to favour the continued development and use of alternatives to blood transfusion. We summarise the current roles of alternatives to blood in the management of medical and surgical anaemias.**

*Lancet* 2013; 381: 1855–65

See **Editorial** page 1789

See **Comment** page 1791

This is the second in a **Series** of three papers about blood transfusion

**Institute of Anaesthesiology, University and University Hospital Zurich, Zurich, Switzerland** (Prof D R Spahn MD); **and Departments of Pathology and Medicine, Stanford University, Stanford, CA, USA** (Prof L T Goodnough MD)

Correspondence to:
Prof Donat R Spahn, Institute of Anaesthesiology, University and University Hospital Zurich, CH-8091 Zurich, Switzerland
**donat.spahn@usz.ch**

## Introduction

Although the safety of blood has improved substantially since the 1980s, when HIV was discovered to be blood transmissible,[1] blood transfusion is an independent risk factor for adverse patient outcomes.[2] Blood transfusions have been associated with increased mortality,[3] increased length of hospital stay related to infections and sepsis,[4] and multi-organ system dysfunction.[5] A recent meta-analysis[6] of 19 prospective, randomised trials comparing restrictive versus liberal transfusions in more than 6000 patients found that adherence to restrictive blood transfusion decreased hospital mortality and postoperative infections. Erythrocyte damage related to duration of blood storage[7] might partly account for these observed adverse patient outcomes. Canine models suggest that old blood has a propensity to haemolyse in vivo, releasing vasoconstrictive cell-free haemoglobin;[8] and post transfusion, patients have decreased deformability of the erythrocyte membrane related to duration of blood storage.[7] Finally, potential known and unknown risks such as transmission of blood-borne pathogens are still concerns;[9] therefore, blood transfusions need to be restricted.

The detection, assessment, and treatment of preoperative anaemia are important in the planning of strategies to minimise allogeneic blood transfusions.[10] Anaemia is the most important risk factor for transfusion,[10] and 30% of surgical patients present preoperatively with anaemia.[3] Additionally, preoperative anaemia (haemoglobin of 100–120 g/L in women and 100–130 g/L in men) has been independently associated with increased mortality and morbidity in patients undergoing non-cardiac surgery.[3] The successful management of preoperative anaemia decreases blood transfusions in patients undergoing orthopaedic[11] and cardiac surgery.[12] The use of algorithm-guided treatment of patients with trauma,[13] and in patients undergoing orthopaedic[11,14] and cardiac surgery[15,16] has been associated with decreased transfusion needs and improved patient outcomes such as complications, length of hospital stay, and mortality.

Strategies to decrease perioperative blood losses are also important, including meticulous surgical technique, use of autologous blood salvage, acute normovolaemic haemodilution, and avoidance of coagulopathy and hypothermia.[17] In addition to blood and patient safety issues, cost needs to be considered: in the USA, when all the activities involved in blood transfusion are considered, the estimated price of transfusion of one blood unit is between US$700–$1200.[18] These costs vary among countries. The administration costs associated with blood transfusion are estimated to be three to five times higher than the purchase costs. We summarise strategies that enable patients to minimise or avoid blood transfusions in the management of surgical and medical anaemias.

## Surgical patients

### Preoperative management

Preoperative planning is essential to reduce or avoid perioperative allogeneic transfusion. A thorough patient history is the best method to discover clinically important disorders in haemostasis—eg, bleeding related to previous surgical and dental procedures, epistaxis, menorrhagia, excessive bleeding with major trauma, and easy bruising or joint or muscle swelling after minor trauma. Figure 1 shows the principles of patient blood management

#### Search strategy and selection criteria

We assessed recent progress to provide a better understanding of best transfusion practices on the basis of evidence-based clinical trials, published clinical practice guidelines, and emerging pathways for improving blood use and clinical patient outcomes. We searched the Cochrane Library, Medline, and Embase for articles published between Jan 1, 2008, and Dec 31, 2012. We used the search terms "blood alternatives", "pharmacologic alternatives to blood", "erythropoiesis-stimulating agents", "recombinant clotting factors"; "haemostasis agents", and "antifibrinolytic agents". We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this article has room for. Our reference list was modified on the basis of comments from peer reviewers. Further information on blood transfusions in specific clinical settings such as stem cell and organ transplantation are available from cited references.

and the use of alternatives to blood. For most non-cardiac surgery procedures, intra-operative tests of the coagulation system are not necessary except in the event of unexpected and substantial bleeding. The most important predictor of need for blood transfusion during surgery is the patient's baseline red blood cell volume. Figure 2 shows how preadmission testing should take place as far in advance as possible (eg, 30 days) of elective surgery to allow time for adequate identification, assessment, and management of anaemia.[10,20] The most frequent, treatable cause of anaemia is iron deficiency.[21] The assessment of anaemia should also consider unexpected diagnoses, including chronic kidney disease or occult malignant disease. This approach needs close collaboration among the patients' primary care physicians, surgeons, anaesthesiologists, and the medical director of the institution's pre-admission testing programme, so that investigation of the elective surgical patient takes place far enough in advance (up to 30 days) to allow management of unexpected anaemia.

Pharmacological alternatives to blood components are important in patient blood management in the surgical setting (figure 2) and in patients with medical anaemias such as anaemia associated with chronic inflammatory disease, chemotherapy-induced anaemias in patients with cancer, and anaemia associated with end-stage chronic kidney disease. The use of erythropoiesis-stimulating agents was first approved to increase the concentration of haemoglobin in patients with chronic kidney disease.[22] Erythropoiesis-stimulating agents were then approved for use in patients undergoing elective surgery on the basis of prospective randomised trials that showed reduced allogeneic blood transfusions in patients undergoing orthopaedic surgery. Management of anaemia with erythropoiesis-stimulating agents or iron in patients undergoing orthopaedic[10,11] or cardiac[12,23] surgery is recommended as a blood-conservation strategy. However, the safety of erythropoiesis-stimulating agents in surgical settings has been reassessed after a post-approval study[24] showed that patients scheduled for elective spine surgery who received preoperative erythropoiesis-stimulating agents had higher rates of thrombosis (assessed with Doppler evaluation) than patients who received placebo.

The role and the safety of erythropoiesis-stimulating agents in the management of preoperative patients with anaemia who are undergoing cardiovascular surgery are unresolved issues. Two European trials[25,26] with 76 and 320 patients showed no differences in mortality, thrombotic events, or serious adverse events between patients given erythropoiesis-stimulating agents and patients given placebo; a substantial reduction in blood transfusions was evident. A US study[27] also concluded that erythropoietic stimulation was well tolerated despite some late deaths in patients given erythropoietic stimulating agent. However, data from this study led the US Food and Drug Administration to restrict the use of erythropoiesis-stimulating agents in the USA in the elective surgical setting to non-vascular, non-cardiac patients undergoing major elective surgery. Similarly, approval for perisurgical

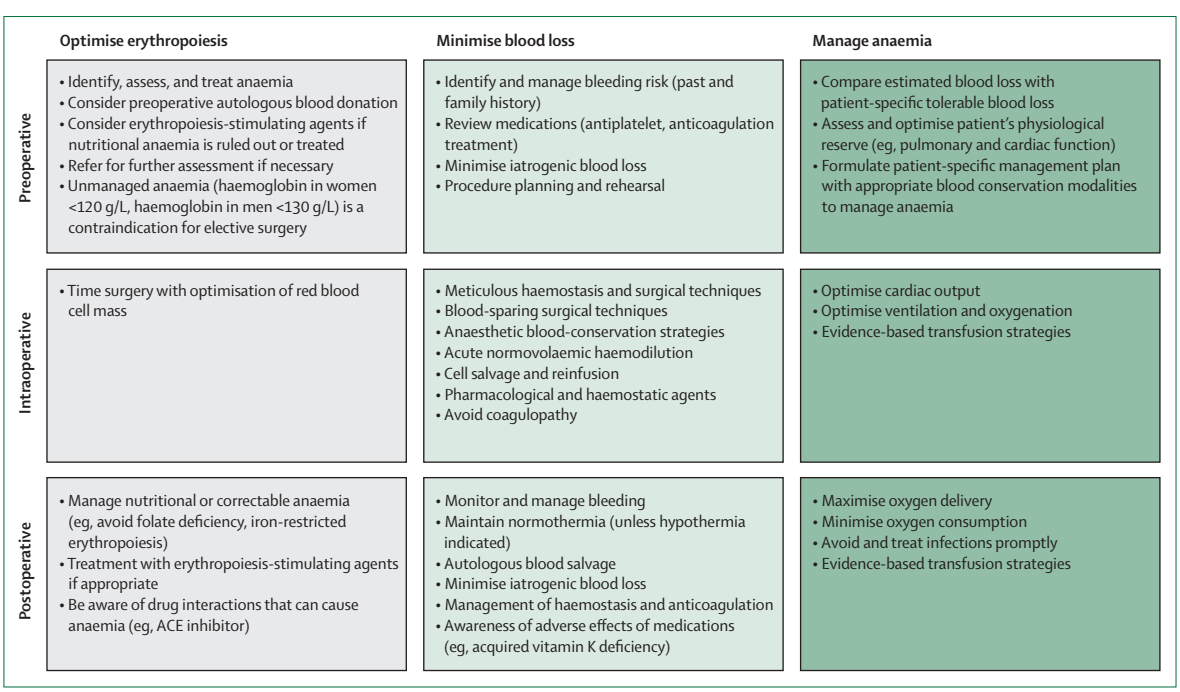



***Figure 1:*** **Patient blood management**
These recommendations apply in the perisurgical period enable treating physicians to have the time and methods to provide patient-centred and evidence-based patient blood management to minimise allogeneic blood transfusions. Modified from Goodnough and Shander,[19] by permission of the American Society of Anesthesiologists.

use of erythropoiesis-stimulating agents in the European Union has been restricted to elective orthopaedic surgical patients. Erythropoiesis-stimulating agents remain a valuable means for patients with special requirements, such as Jehovah's Witness patients, for whom blood transfusion is not an option.[28] However, until additional safety data are available, the off-label use of erythropoiesis-stimulating agents in patients undergoing cardiac or vascular surgery cannot be supported.

Since the 1980s, preoperative autologous donation has been a common practice in elective surgical settings such as total joint replacement. In 1992, more than 6% of the blood transfused in the USA was autologous.[29] Subsequent improvements in blood safety have been accompanied by a decreased interest in preoperative autologous donation.[30] Nevertheless, preoperative autologous donation remains a potential strategy for patients undergoing elective surgery because of its conservation of allogeneic blood inventory, its value in patients with red blood cell alloantibodies, and the potential to limit exposure to emerging blood pathogens. The most recent example of an emerging blood pathogen is the West Nile virus, in which the Centers for Disease Control and Prevention recommended deferral of elective surgery or use of preoperative autologous donation pending implementation of a screening test for the pathogen. However, preoperative autologous donation is not recommended in procedures that are unlikely to need transfusion (eg, vaginal hysterectomy, transurethral resection of the prostate, and rhinoplasty)—ie, the less than 10% of cases, for which cross-matched blood would not be ordered.

The increased costs associated with preoperative autologous donation, the reduced risk of infection associated with allogeneic blood transfusions, and advances in surgical techniques to reduce blood loss have made preoperative autologous donation poorly cost effective. In a controlled trial of non-anaemic patients who predonated two autologous blood units before total hip replacement surgery, none of the patients, including the control cohort, received allogeneic blood; however, two-thirds of the patients in the preoperative autologous donation cohort received their autologous blood, for an additional cost of $758 per patient.[31] Preoperative autologous donation might be appropriate for substantial procedures (eg, total hip revision or scoliosis repair) and for patients with serologic alloantibodies to blood.[30]

## Management of blood loss anaemia

### Perioperative autologous blood procurement

Acute normovolaemic haemodilution is the removal of whole blood from a patient while the circulating blood volume is restored with an acellular fluid shortly before

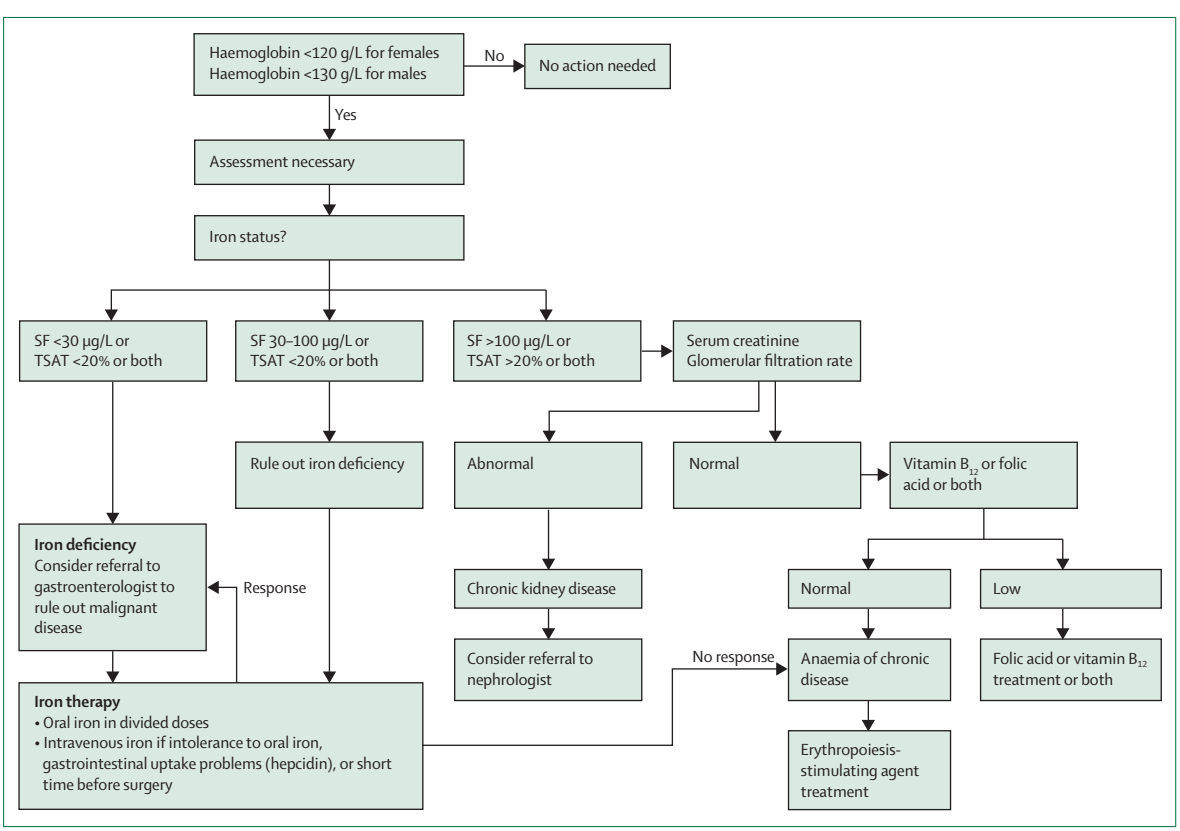



*Figure 2:* **Algorithm for the detection, assessment, and management of preoperative anaemia**
SF=serum ferritin. TSAT=transferrin saturation. Modified from Goodnough and colleagues,[10] by permission of Oxford Journals.

substantial surgical blood loss. Blood units are reinfused in the reverse order of collection because the first unit collected and the last unit transfused have the highest concentration of red blood cells, coagulation factors, and platelets. The benefit of acute normovolaemic haemodilution is the reduction of blood loss when whole blood is shed perioperatively at lower haematocrit values achieved with acute normovolaemic haemodilution. Because blood collected by acute normovolaemic haemodilution is stored at room temperature in the operating room and is returned to the patient within 8 h of collection, platelets and coagulation factors remain functional. Additionally, unit testing is not essential. Acute normovolemic haemodilution is cheaper but equivalent to preoperative autologous donation in selected clinical settings (eg, patients with a high preoperative haemoglobin concentration undergoing a surgical procedure with a high expected blood loss such as a revision hip replacement), for reduction of allogeneic blood transfusions.[29] Other outcomes including anaesthesia and surgery times, intraoperative haemodynamic values, and length of hospital stay were also similar for preoperative autologous donation and acute normovolaemic haemodilution. Low-volume acute normovolaemic haemodilution did not reduce allogeneic blood for patients undergoing cardiac value replacement surgery.[32] Except for patients undergoing open heart coronary artery bypass surgery and Jehovah's Witnesses, there is no presently defined role for acute normovolaemic haemodilution.

As with preoperative autologous donation and acute normovolaemic haemodilution, the safety and efficacy of autologous blood salvage has undergone scrutiny. A controlled study in patients undergoing cardiothoracic surgery showed little efficacy when transfusion requirements and clinical outcomes were followed.[33] Collection of the equivalent of one blood unit is possible for less expensive methods with unwashed blood, but at least two blood units need to be recovered with a cell-saver instrument with washed blood in order to achieve cost-effectiveness. Therefore, this technology is useful in cost savings and blood-inventory conservation for patients with substantial blood loss.[34,35] However, the above cost calculations only took into account the product cost and not the costs related to administration of blood.[17] If full costs of blood administration are considered, autologous blood procurement becomes more cost effective.[18]

### Cardiac surgery

In cardiac surgery, perioperative assays for platelet count, haemoglobin concentration, and coagulation abnormalities are obtained, and treatment should be guided by results. Point-of-care devices to monitor coagulation, coupled with treatment algorithms for pharmacological and transfusion treatment, have roles in liver transplantation, cardiac,[15,16] and trauma[13] surgery. In a prospective randomised study in patients undergoing aortic surgery with clinically relevant coagulopathic bleeding after cardiopulmonary bypass, the administration of fibrinogen guided by thrombelastometry decreased overall transfusion needs from 13 to 2 units of allogeneic blood products ($p<0·001$) and increased the percentage of patients who avoided all allogeneic blood products from 0–45% ($p<0·001$).[16]

For patients with qualitative platelet function abnormalities, desmopressin promotes platelet aggregation through the release of von Willebrand factor from the endothelium and was initially approved for the treatment of von Willebrand disease. Meta-analyses of clinical trials in patients without von Willebrand disease undergoing surgery have shown a trend in reducing the need for allogeneic blood transfusions[36] with only a small reduction in blood transfusions[37] with desmopressin treatment. In particular, patients with impaired platelet function[38] or those on platelet inhibitors[39] might benefit from treatment with desmopressin. The drug also improves platelet function in the presence of hypothermia and acidosis.[40] Initial concerns regarding increased thrombotic complications were not confirmed in more recent meta-analyses.[37] The routine use of desmopressin as a prophylactic agent is still debated in cardiac surgeries, and is not presently recommended.[23]

Point-of-care testing-based transfusion algorithms show promise in the identification of real-time coagulopathies that can be given targeted treatment.[41] A retrospective cohort study done at University Hospital Essen, Germany, reviewed 3865 patients undergoing cardiac surgery and the incidence of intraoperative allogeneic blood transfusion before and after implementation of point-of-care testing assays including activated clotting time, thromboelastometry, and whole-blood impedance aggregometry (also called multiple electrode aggregometry). Algorithm implementation after point-of-care testing allowed for the transfusion of plasma, platelets, fibrinogen concentrate, and prothrombin complex concentrate only after abnormal point-of-care testing values were obtained. Findings showed a significant decrease in blood and plasma transfusions, a significant increase in platelet, fibrinogen concentrate, and prothrombin complex concentrate administration, and reduction by 50% of rates of re-operation for bleeding and for thrombotic complications.

Antifibrinolytic agents have been used to reduce blood loss in patients undergoing complex open heart procedures. Antifibrinolytics inhibit the physiological fibrinolytic pathway, which is responsible for limiting and dissolving clots. Aminocaproic acid reduces blood loss and blood transfusions in patients undergoing cardiac surgery.[42] Aprotinin was removed from the market in 2007, but a re-investgation of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study[43] and other data have led to a reversal of this decision and plans exist for the reintroduction of aprotinin in Canada and the European Union for patients undergoing cardiac surgery.[44]

A Cochrane review concluded that antifibrinolytics provide worthwhile reductions in blood loss and allogeneic blood transfusions; and that although aprotinin seems to be slightly more effective, the lysine analogues seem to have no serious adverse events.[45] A meta-analysis of studies including more than 10 000 patients has shown that the lysine analogue tranexamic acid reduces the need for transfusion in patients undergoing surgery.[46] In a clinical trial (CRASH 2) of 20 000 patients with trauma,[47] early administration of 1 g tranexamic acid before an 8-h infusion of another gram resulted in a decrease in mortality and thrombotic complications, if treatment was started within the first 3 h after trauma.

Fibrinogen has a central role in the formation of the platelet plug.[48] Recent recommendations call for a minimum fibrinogen concentration of 1·5–2·0 g/L in surgical patients[49,50] and for a fibrinogen concentration of more than 2·0 g/L in postpartum bleeding.[51] Treatment with fibrinogen concentrates is more effective than conventional treatment with plasma in the repletion of fibrinogen concentrations in patients with haemorrhage.[52] In a prospective randomised study in patients undergoing coronary artery bypass surgery 2 g of fibrinogen decreased blood loss and the decrease in haemoglobin postoperatively.[53] Finally, in a prospective randomised study in patients undergoing aortic surgery with clinically relevant coagulopathic bleeding after cardiopulmonary bypass, administration of fibrinogen guided by thrombelastometry decreased overall transfusion needs from 13 to 2 units of allogeneic blood products ($p<0·001$).[16] Although reports have been published on the use of fibrinogen concentrate as a haemostatic agent, evidence for the usefulness of this treatment is not yet conclusive in all surgery specialties.

### Trauma

Patients with blunt or penetrating trauma and massive haemorrhage need complex resuscitation to address dilutional and consumptive coagulopathies that are often accompanied by hypothermia and acidosis.[54] Point-of-care testing has enabled analysis of these coagulation abnormalities in the setting of major trauma. Rugeri and colleagues[55] did a prospective observational study in which 90 patients with trauma underwent standard coagulation assays along with thrombelastometry. Their data showed the ability of point-of-care testing technology to rapidly detect in-vivo coagulopathic changes in these patients.

Rapid thrombelastography was shown to be better than conventional coagulation tests in the prediction of transfusion needs in nearly 2000 trauma patients.[50] A meta-analysis concluded that point-of-care testing had a substantial effect on the amount of bleeding in massively transfused patients, but did not show improvement in morbidity or mortality.[56] More studies are needed to further investigate the role of point-of-care testing in the diagnosis and treatment of coagulopathy in patients with trauma. Further studies are also needed to assess the appropriateness and optimisation of early goal-directed treatment in patients with coagulopathic trauma, and to find out if component-specific treatment could improve present transfusion protocols, reduce transfusion-associated complications, and improve coagulopathy-related morbidity and mortality.

Prothrombin complex concentrates are increasingly used off-label in trauma and surgical settings associated with coagulopathy.[49] Targeted treatment with prothrombin complex concentrates with rotation thrombelastometry-based algorithms has shown significant reductions in transfused blood components.[57] Nevertheless, the role of prothrombin complex concentrates in perioperative-related bleeding remains uncertain.[58] To avoid thrombotic complications, care should be taken to avoid excessive treatment via accurate monitoring of patients' coagulation status.

### Inherited and acquired coagulopathies

A history of bleeding episodes or physical signs of bleeding mandate a full bleeding workup and consultation with a haematologist to assess platelet numbers and function and the presence of inherited or acquired coagulation factor deficiencies. The patient's medication profile can reveal inhibitory drugs, such as aspirin or aspirin-containing compounds, non-steroidal anti-inflammatory drugs, warfarin, chronic steroid use, platelet inhibitors, oral antithrombin or Xa anticoagulants, or low molecular weight heparin. The history might also reveal acquired coagulation disorders associated with parenchymal liver disease, renal failure, or myeloproliferative syndromes.

Prothrombin complex concentrates, one-factor concentrates, and recombinant coagulation factors are approved for use in patients with inherited coagulation factor deficiencies. Some of these products have been approved as haemostatic agents in patients with acquired coagulopathies, such as the management of acute reversal of warfarin coagulopathy , alongside vitamin K treatment.[59] Prothrombin complex concentrates that contain all four (II, IX, X, and VII) of the vitamin K-dependent clotting factors are approved internationally, including the USA. Three-factor prothrombin complex concentrates are approved only for the replacement of factor IX; therefore, the use of these three-factor prothrombin complex concentrates for reversal of warfarin is controversial.[59]

The safety of prothrombin complex concentrates compared with plasma is a subject of debate.[59] In the setting of emergency reversal of warfarin coagulopathy, a review of eight clinical studies[60] identified a thromboembolic event rate of 0·9% associated with treatment with prothrombin complex concentrates. These thrombotic events arose during emergency reversal of anticoagulation in patients with a high thrombosis risk attributable to underlying disease. Guidelines from several medical societies on the use of prothrombin complex concentrates for acute warfarin reversal have been published[59] and have recommended that prothrombin complex concentrates be

given as an alternative to fresh frozen plasma. The most recently updated guidelines from the American College of Chest Physicians[61] recommend treatment with prothrombin complex concentrates instead of plasma for acute reversal of warfarin coagulopathy. The uncertain role of prothrombin complex concentrates in comparison with treatment with plasma for acute warfarin reversal is partly attributable to the variability in the contents and amount of clotting factors in these preparations;[59] regulatory approval status for different countries; scarcity among hospital formularies, particularly in small community hospitals; and potential risks of thrombogenicity in patients with an underlying disease who have a high thrombotic potential.

Recombinant activated factor VII complexes directly with tissue factor released from the subendothelium at sites of vascular disruption. Recombinant activated factor VII also binds to activated platelets, which concentrates factor X activation to sites of tissue injury. Approved indications of recombinant activated factor VII are treatment of bleeding episodes (or prevention of bleeding from invasive procedures) in patients with congenital haemophilia A or haemophilia B who have inhibitors to factors VIII or IX; patients with congenital factor VII deficiency; and in patients with acquired haemophilia. Additionally, in the European Union, recombinant activated factor VII is approved for patients with inherited qualitative platelet defects. However, these approved indications accounted for only 3121 (4·2%) of 73747 cases reported to use recombinant activated factor VII in the USA from 2000–08.[62] A systematic literature review found little evidence of efficacy for five off-label clinical settings (intracranial haemorrhage, cardiac surgery, trauma, liver transplantation, and prostatectomy), with no mortality reduction associated with use of recombinant activated factor VII in these settings.[63]

The safety profile of recombinant activated factor VII suggests an increased risk of thrombotic arterial events that might be under-reported by treating physicians. Levi and colleagues[64] analysed 35 randomised trials with 4468 patients including patients with haemophilia with inhibitors to factors VIII or IX, and off-label settings such as trauma, liver transplantation, and patients with gastrointestinal bleeding caused by cirrhosis. Investigators found that 11·1% of patients had thromboembolic events. Rates of venous thromboembolic events were similar for patients who received recombinant activated factor VII (5·3%) compared with patients given placebo (5·7%); however, arterial events were significantly higher (5·5% *vs* 3·2%, p<0·003) in patients older than 75 years of age who were receiving recombinant activated factor VII than in patients given placebo.

### New alternatives in development

Factor XIII is activated by thrombin and crosslinks soluble fibrin monomers into insoluble fibrin strands. Additionally, activated factor XIII protects the developing clot from fibrinolysis and has important roles in wound healing.[65] Low concentrations of factor XIII (<60% in neurosurgery and <70% in cardiac surgery) are associated with postoperative haemorrhage, and replacement treatment has been shown to reduce postoperative bleeding.[66,67] Factor XIII also decreased transfusion needs in patients at high risk of intraoperative bleeding.[68] Therefore, the perioperative monitoring and targeted replacement of factor XIII concentrations is a promising approach to decrease transfusion needs and postoperative bleeding. Factor XIII has been recommended as a haemostatic agent to stabilise clots in patients bleeding after cardiac surgery, when other treatments have not yielded satisfactory results.[23] The source of factor XIII varies according to local availability: factor XIII concentrate, cryoprecipitate, or plasma. Human recombinant factor XIII is approved and has been successfully used in the treatment of congenital factor XIII deficiency,[69] but is not yet approved for patients with acquired factor XIII deficiency.[65] More data are needed to justify the routine use of human recombinant factor XIII as a haemostatic agent.

The use of topical haemostatics continues to evolve and enter clinical practice at a rapid rate.[70] Although reports exist of antibody formation against bovine coagulation factors with cross-reactivity to human coagulation factors resulting in coagulopathy, this has not been seen with products containing (recombinant) human thrombin.[71] These agents can be especially useful when access to the bleeding site is difficult.[72] A controlled study in patients undergoing cardiac surgery has shown that use of topical haemostatics can result in less blood loss and fewer transfusions.[73]

## Medical anaemias

### Anaemia of chronic disease

The Circular of Information for the Use of Human Blood and Blood Components identifies four haematinics that should be given instead of a blood transfusion, when appropriate: iron, folate, vitamin $B_{12}$, and erythropoietin.[22] With molecular biology, our understanding of the pathophysiology of anaemia of chronic disease has improved substantially. While sequestration of iron has long been known to be central to the pathogenesis of the anaemia of chronic disease, it is now known that the regulation of iron homoeostasis is through hepcidin, as the central regulator of gastrointestinal iron absorption, iron storage in macrophages, and resultant plasma iron concentration.[74] Iron sequestration mediated by hepcidin is a common cause of iron-restricted erythropoiesis in patients with inflammation. Hepcidin acts to sequester iron by inhibiting the exit of storage iron from hepatocytes and macrophages into plasma, and also absorption of dietary iron from duodenal enterocytes. Hepcidin binds and degrades the iron exporter ferroportin, and thereby reduces the iron available for erythropoiesis.

Hepcidin production is regulated under normal conditions by iron stores and erythropoietic activity.

Increased plasma and storage iron stimulate hepcidin production, which in turn inhibits dietary iron absorption. Conversely, iron deficiency and increased erythropoietic activity (eg, myelodysplastic syndromes or haemolytic anaemias) suppress hepcidin to very low concentrations, which allows increased absorption of dietary iron and release of iron storage and increased haemoglobin synthesis.[75] The mechanisms by which erythropoiesis affects hepcidin production are not well understood, but both direct and indirect effects of anaemia and erythropoiesis might play a part. Candidate mediators include soluble factors released by erythroid precursors, and decreased circulating or stored iron.[76] Hypoxia can change hepcidin production directly through hypoxia-inducible factor or indirectly via increased erythropoietin production and erythropoiesis.[77] Hepcidin concentrations are high in several inflammatory diseases including rheumatological diseases, inflammatory bowel disease, infections, critical illness, and malignant diseases.[75] Increased hepcidin concentrations cause the retention of iron in macrophages and enterocytes, leading to hypoferraemia, iron-restricted erythropoiesis, and decreased responsiveness to treatment with erythropoiesis-stimulating agents. The development and commercial availability of an accurate and reproducible immunoassay for human hepcidin has improved our understanding of the pathogenic role of hepcidin in a range of iron disorders, and in the future, might be useful in the identification of patients with iron-restricted erythropoiesis who are intolerant or unresponsive to oral iron, and for whom treatment with IV iron might be needed to correct the anaemia.[78,79]

Several clinical trials were undertaken in an attempt to show improved clinical outcomes in patients given erythropoiesis-stimulating agents for anaemia associated with inflammation, such as chronic kidney disease or cancer (table).[24,43,80–91] Aggressive management of anaemia in the cohorts given erythropoiesis-stimulating agents was associated with increased morbidity (thrombosis or cardiovascular events) and increased mortality. Literature reviews and meta-analyses of trials of erythropoiesis-stimulating agents for both approved and off-label oncology settings have analysed survival and other safety outcomes.[92] The mechanisms behind the association between increased morbidity and mortality outcomes and erythropoiesis-stimulating agents are unclear. One hypothesis is that erythropoiesis-stimulating agents stimulate disease progression or thrombosis or both by activation of erythropoietin receptors present on tumour cells or associated vascular endothelium.[93] However, other investigators have found no evidence that erythropoietin receptors are functionally expressed on tumours[94] or are present on non-haemopoietic cells.[95]

On the basis of this evidence, use of erythropoiesis-stimulating agents in chronic kidney disease and cancer has been affected by updates in guidelines[96,97] and revised labels that show safety concerns[98] for target haemoglobin concentrations. In these patients, treatment with erythropoiesis-stimulating agents should only be initiated when concentrations of haemoglobin are less than 100 g/L or in patients with symptomatic anaemia. In this setting, a low dose of erythropoiesis-stimulating agent is given to produce red cell responses sufficient for patients to avoid allogeneic blood transfusions. In clinical practice, the increased risks of death and thromboembolic events should be balanced against the benefits of reduced exposure to blood transfusions with long-term treatment with erythropoiesis-stimulating agents, and needs to take into account each patient's clinical circumstances and preferences.[99] Strategies to extend the labelled indications for erythropoiesis-stimulating agents into other patient populations such as in congestive heart failure have been unsuccessful; in a recent study, treatment with erythropoiesis-stimulating agents did not improve clinical outcomes in patients with systolic heart failure and mild to moderate anaemia.[100]

## Iron-restricted erythropoiesis

The most common cause of inappropriate blood transfusion on medical services is the transfusion of patients for iron-deficiency anaemia. Absolute deficiency of storage iron is the most common cause of iron-restricted erythropoiesis, especially in young children, pregnant women, premenopausal women, and elderly people.[101] 11% of men and 10·2% of women aged 65 years and

| | Target control (haemoglobin g/L) | Reference, year | Clinical outcomes |
|---|---|---|---|
| **Surgery** | | | |
| SPINE | <130 | Stowell, 2009[23] | Increased thrombosis |
| **Chronic kidney disease** | | | |
| Dialysis *vs* predialysis | ≥130 *vs* 100 | Besarab, 1998[80] | Decreased OS |
| CHOIR | 135 *vs* 113 | Singh, 2006[81] | Decreased OS |
| CREATE | 130–150 *vs* 105–115 | Drueke, 2006[82] | Decreased OS |
| TREAT | 130 *vs* 90 | Pfeffer, 2006[83] | Decreased OS |
| **Oncology** | | | |
| Chemotherapy | | | |
| Lymphoma | ≥140–150 (F,M) | Hedenus, 2003[84] | Decreased OS |
| Breast (BEST) | >140 | Leyland-Jones, 2005[85] | Decreased OS |
| Breast (PREPARE) | ≥130 | Untch, 2011[86] | Increased thrombosis |
| Radiotherapy | | | |
| Head and neck (ENHANCE) | ≥140–150 (F,M) | Henke, 2003[87] | Decreased OS |
| Head and neck (DAHANCA) | >155 | Overgaard, 2007[88] | Decreased disease-free survival |
| Chemotherapy and radiotherapy | | | |
| (Gynecologic Oncology) | >140 | Thomas, 2008[89] | Decreased OS |
| **No or palliative treatment** | | | |
| Non-small cell lung | ≥140 | Wright, 2007[90] | Decreased OS |
| Non-myeloid cancer | ≥130 | Smith, 2008[91] | Decreased OS |

OS=overall survival. F=female. M=male. Reproduced from Goodnough and Shander,[44] by permission of the International Anesthesia Research Society.

*Table:* **Post-approval clinical trials of erythropoiesis-stimulating agents**

older are anaemic, with an overall rate of more than 20% at age 85 years and older. Of older people with anaemia, a third are nutritionally deficient, with absolute iron deficiency being the most common aetiology of these.[102] Ageing is a pro-inflammatory state, in which iron absorption in the elderly might be impaired because of a hepcidin-mediated effect.

Blood loss (eg, in females with menses, gastrointestinal lesions, or community blood donors) is the main cause of iron deficiency and is important, not only because of its prevalence, but because proper diagnosis and management of the bleeding lesion is important.[103] Therapeutic management, after any pathological cause of blood loss has been considered, is focused mainly on repletion of iron stores. Most patients with iron deficiencies respond well to oral iron treatment, but intravenous iron might be necessary when hepcidin-mediated mechanisms inhibit oral iron absorption in the presence of inflammation.[21]

Iron-restricted erythropoiesis can happen with absolute iron deficiency, functional iron deficiency, or, as described above, under anaemia of chronic disease and iron sequestration.[21] Most individuals with an absolute iron deficiency without inflammation respond well to oral iron treatment, but intravenous iron might be necessary in patients with inflammation-mediated hepcidin effects.[20] Functional iron deficiency can arise in patients with substantial erythropoietin-mediated erythropoiesis or upon treatment with erythropoiesis-stimulating agents, seen by a reduction in transferrin saturation in patients with cancer and in patients with chronic kidney disease undergoing dialysis treatment. Functional iron deficiency can be ameliorated with IV iron treatment.[21] An algorithm approach for the assessment and management of anaemia based on initial assessment of iron status has been recommended by a consortium of European societies for patients scheduled for elective surgery (figure 2).[10]

IV iron has been recommended for the management of anaemia in patients with chronic kidney disease who are unresponsive to erythropoiesis-stimulating agents.[97] Studies in patients with cancer with chemotherapy-induced anaemia who are given erythropoiesis-stimulating agents found significant improvements in haemoglobin concentrations and hematopoietic responses in patients given IV iron compared with those receiving oral iron or no iron.[104] The low but defined risks of IV iron, along with current labelled indications that restrict use in patients with end-stage renal disease for various preparations, have ensured that the role of IV iron outside the setting of renal dialysis patients remains in evolution.

## Conclusions

Since the recognition that non-A, non-B hepatitis, and HIV were transmissible by blood transfusion, the benefit/risk profile and use of alternatives to blood have been driven by risks related to blood transfusion. The role of the alternatives to blood need to be better defined by patient-centred treatment plans based on anticipated perioperative blood loss and likelihood of blood transfusion The presence of preoperative anaemia, the type of surgical procedure, the likelihood of coagulopathy, and patient comorbidities will further affect the need for blood transfusion or its alternatives. The successful use of point-of-care testing suggests that more targeted treatment can improve patient outcomes such as multi-organ system failure associated with trauma and blood transfusions.[105] In this context, randomised prospective trials are needed. The success of the CRASH 2 study[47] that used early anti-fibrinolytic treatment in patients with trauma, suggests that more targeted treatments to address associated coagulopathies such as prothrombin concentrates (II, VII, IX, and X), fibrinogen concentrates, recombinant factor VIIa, or recombinant XIII might be of value in specific patient settings. Potential future areas of research include point-of-care testing coupled with therapeutic algorithms. Quality indicators measuring patient outcomes (ie, hospital stay and mortality) need to be used so that the alternatives to blood transfusion can be more effectively assessed and incorporated into clinical practice.

### Contributors

DRS and LTG researched, drafted, and wrote the review jointly.

### Conflicts of interest

DRS's academic department is receiving grant support from the Swiss National Science Foundation (Bern, Switzerland), the Swiss Society of Anaesthesiology and Reanimation (Bern, Switzerland), the Swiss Foundation for Anesthesia Research (Zurich, Switzerland), Bundesprogramm Chancengleichheit (Bern, Switzerland), CSL Behring (Bern, Switzerland), and Vifor SA (Villars-sur-Glâne, Switzerland). In the past 5 years, DRS has received honoraria or travel support for consulting or lecturing from the following companies: AMGEN GmbH (Munich, Germany), Baxter AG (Volketswil, Switzerland), Baxter S.p.A. (Rome, Italy), CSL Behring GmbH (Hattersheim am Main, Germany and Bern, Switzerland), Ethicon Biosurgery (Sommerville, NJ, USA), Janssen-Cilag AG (Baar, Switzerland), Janssen-Cilag EMEA (Beerse, Belgium), Novo Nordisk A/S, (Bagsvärd, Denmark), Octapharma AG (Lachen, Switzerland), Organon AG (Pfäffikon, Switzerland), Oxygen Biotherapeutics (Costa Mesa, CA, USA), Pentapharm GmbH (now tem Innovations GmbH; Munich, Germany), ratiopharm Arzneimittel Vertriebs-GmbH (Vienna, Austria), Roche Pharma (Switzerland) AG (Reinach, Switzerland), Vifor Pharma Deutschland GmbH (Munich, Germany), Vifor Pharma Österreich GmbH (Vienna, Austria), Vifor (International) AG (St Gallen, Switzerland). LTG is a consultant for Amgen (Thousand Oaks, CA, USA), Luitpold (Shirley, NY, USA), Vifor (Glattbrugg, Switzerland), CSL Behring (King of Prussia, PA, USA), Hemocue (Cypress, CA, USA), and Octapharma (Hoboken, NJ, USA).

### Acknowledgments

Jason Calcagno provided invaluable assistance in preparation of this manuscript.

### References

1 Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA* 2003; **289:** 959–62.
2 Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. *Transfus Med Rev* 2011; **25:** 89–101.
3 Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011; **378:** 1396–407.
4 Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. *J Am Coll Surg* 2009; **208:** 931–37.

5 Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; **288:** 1499–507.

6 Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012; **4:** CD002042.

7 Frank SM, Abazyan B, Ono M, et al. Decreased erythrocyte deformability after transfusion and the effects of erythrocyte storage duration. *Anesth Analg* 2013; **116:** 975–81.

8 Solomon SB, Wang D, Sun J, et al. Mortality increases after massive exchange transfusion with older stored blood in canines with experimental pneumonia. *Blood* 2013; **121:** 1663–72.

9 Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; **113:** 3406–17.

10 Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth* 2011; **106:** 13–22.

11 Na HS, Shin SY, Hwang JY, Jeon YT, Kim CS, Do SH. Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. *Transfusion* 2011; **51:** 118–24.

12 Yoo YC, Shim JK, Kim JC, Jo YY, Lee JH, Kwak YL. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. *Anesthesiology* 2011; **115:** 929–37.

13 Schochl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011; **15:** R83.

14 Kotze A, Carter LA, Scally AJ. Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle. *Br J Anaesth* 2012; **108:** 943–52.

15 Weber CF, Gorlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology* 2012; **117:** 531–47.

16 Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology* 2013; **118:** 40–50.

17 Shander A, Van Aken H, Colomina MJ, et al. Patient blood management in Europe. *Br J Anaesth* 2012; **109:** 55–68.

18 Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; **50**: 753–65.

19 Goodnough LT, Shander A. Patient blood management. *Anesthesiology* 2012; **116:** 1367–76.

20 Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010; **116:** 4754–61.

21 Goodnough LT. Iron deficiency syndromes and iron-restricted erythropoiesis. *Transfusion* 2012; **52:** 1584–92.

22 Goodnough LT, Monk TG, Andriole GL. Erythropoietin therapy. *N Engl J Med* 1997; **336:** 933–38.

23 Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011; **91:** 944–82.

24 Stowell CP, Jones SC, Enny C, Langholff W, Leitz G. An open-label, randomized, parallel-group study of perioperative epoetin alfa versus standard of care for blood conservation in major elective spinal surgery: safety analysis. *Spine* 2009; **34:** 2479–85.

25 Sowade O, Warnke H, Scigalla P, et al. Avoidance of allogeneic blood transfusions by treatment with epoetin beta (recombinant human erythropoietin) in patients undergoing open-heart surgery. *Blood* 1997; **89:** 411–18.

26 Weltert L, D'Alessandro S, Nardella S, et al. Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: a randomized blind controlled study. *J Thorac Cardiovasc Surg* 2010; **139:** 621–26.

27 D'Ambra MN, Gray RJ, Hillman R, et al. Effect of recombinant human erythropoietin on transfusion risk in coronary bypass patients. *Ann Thorac Surg* 1997; **64:** 1686–93.

28 Goodnough LT, Shander A, Spence R. Bloodless medicine: clinical care without allogeneic blood transfusion. *Transfusion* 2003; **43:** 668–76.

29 Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. Second of two parts: blood conservation. *N Engl J Med* 1999; **340:** 525–33.

30 Brecher ME, Goodnough LT. The rise and fall of preoperative autologous blood donation. *Transfusion* 2001; **41:** 1459–62.

31 Billote DB, Glisson SN, Green D, Wixson RL. A prospective, randomized study of preoperative autologous donation for hip replacement surgery. *J Bone Joint Surg Am* 2002; **84**: 1299–304.

32 Virmani S, Tempe DK, Pandey BC, et al. Acute normovolemic hemodilution is not beneficial in patients undergoing primary elective valve surgery. *Ann Card Anaesth* 2010; **13:** 34–38.

33 Bell K, Stott K, Sinclair CJ, Walker WS, Gillon J. A controlled trial of intra-operative autologous transfusion in cardiothoracic surgery measuring effect on transfusion requirements and clinical outcome. *Transfus Med* 1992; **2:** 295–300.

34 Weltert L, Nardella S, Rondinelli MB, Pierelli L, De Paulis R. Reduction of allogeneic red blood cell usage during cardiac surgery by an integrated intra- and postoperative blood salvage strategy: results of a randomized comparison. *Transfusion* 2013; **53:** 790–97.

35 Carless PA, Henry DA, Moxey AJ, O'Connell D L, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2006; **4:** CD001888.

36 Carless PA, Henry DA, Moxey AJ, et al. Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2004; **1:** CD001884.

37 Crescenzi G, Landoni G, Biondi-Zoccai G, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. *Anesthesiology* 2008; **109:** 1063–76.

38 Steinlechner B, Zeidler P, Base E, et al. Patients with severe aortic valve stenosis and impaired platelet function benefit from preoperative desmopressin infusion. *Ann Thorac Surg* 2011; **91:** 1420–26.

39 Reiter RA, Mayr F, Blazicek H, et al. Desmopressin antagonizes the in vitro platelet dysfunction induced by GPIIb/IIIa inhibitors and aspirin. *Blood* 2003; **102:** 4594–99.

40 Hanke AA, Dellweg C, Kienbaum P, Weber CF, Gorlinger K, Rahe-Meyer N. Effects of desmopressin on platelet function under conditions of hypothermia and acidosis: an in vitro study using multiple electrode aggregometry*. *Anaesthesia* 2010; **65:** 688–91.

41 Gorlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* 2011; **115:** 1179–91.

42 Hutton B, Joseph L, Fergusson D, Mazer CD, Shapiro S, Tinmouth A. Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. *BMJ* 2012; **345:** e5798.

43 Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358:** 2319–31.

44 Goodnough LT, Shander A. Current status of pharmacologic therapies in patient blood management. *Anesth Analg* 2013; **116:** 15–34.

45 Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; **3:** CD001886.

46 Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054.

47 Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377:** 1096–101.

48 Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008; **359:** 938–49.

49 Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013, **17:** R76.

50 Holcomb JB, Minei KM, Scerbo ML, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. *Ann Surg* 2012; **256:** 476–86.

51 Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth* 2012; **108:** 984–89.

52 Kozek-Langenecker S, Sorensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care* 2011; **15:** R239.

53 Karlsson M, Ternstrom L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost* 2009; **102:** 137–44.

54 Goodnough LT, Spain DA, Maggio P. Logistics of transfusion support for patients with massive hemorrhage. *Curr Opin Anaesthesiol* 2013; **26:** 208–14.

55 Rugeri L, Levrat A, David JS, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* 2007; **5:** 289–95.

56 Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; **3:** CD007871.

57 Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. *Injury* 2013; **44:** 209–16.

58 Sorensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R. Clinical review: prothrombin complex concentrates—evaluation of safety and thrombogenicity. *Crit Care* 2011; **15:** R201.

59 Goodnough LT, Shander A. How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood* 2011; **117:** 6091–99.

60 Franchini M, Lippi G. Prothrombin complex concentrates: an update. *Blood Transfus* 2010; **8:** 149–54.

61 Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (suppl 2): 7–47.

62 Logan AC, Yank V, Stafford RS. Off-Label Use of Recombinant Factor VIIa in U.S. Hospitals: Analysis of Hospital Records. *Ann Intern Med* 2011; **154:** 516–22.

63 Yank V, Tuohy CV, Logan AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; **154:** 529–40.

64 Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010; **363:** 1791–800.

65 Levy JH, Greenberg C. Biology of Factor XIII and clinical manifestations of Factor XIII deficiency. *Transfusion* 2012; published online Aug 28. DOI:10.1111/j.1537-2995.2012.03865.x.

66 Godje O, Gallmeier U, Schelian M, Grunewald M, Mair H. Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. *Thorac Cardiovasc Surg* 2006; **54:** 26–33.

67 Gerlach R, Tolle F, Raabe A, Zimmermann M, Siegemund A, Seifert V. Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity: implications of a prospective study. *Stroke* 2002; **33:** 1618–23.

68 Korte WC, Szadkowski C, Gahler A, et al. Factor XIII substitution in surgical cancer patients at high risk for intraoperative bleeding. *Anesthesiology* 2009; **110:** 239–45.

69 Inbal A, Oldenburg J, Carcao M, Rosholm A, Tehranchi R, Nugent D. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012; **119:** 5111–17.

70 Spotnitz WD, Burks S. Hemostats, sealants, and adhesives III: a new update as well as cost and regulatory considerations for components of the surgical toolbox. *Transfusion* 2012; **52:** 2243–55.

71 Singla NK, Gasparis AP, Ballard JL, et al. Immunogenicity and safety of re-exposure to recombinant human thrombin in surgical hemostasis. *J Am Coll Surg* 2011; **213:** 722–27.

72 Gruen RL, Brohi K, Schreiber M, et al. Haemorrhage control in severely injured patients. *Lancet* 2012; **380:** 1099–108.

73 Nasso G, Piancone F, Bonifazi R, et al. Prospective, randomized clinical trial of the FloSeal matrix sealant in cardiac surgery. *Ann Thorac Surg* 2009; **88:** 1520–26.

74 Ganz T. Hepcidin and iron regulation, 10 years later. *Blood* 2011; **117:** 4425–33.

75 Nemeth E. Targeting the hepcidin-ferroportin axis in the diagnosis and treatment of anemias. *Adv Hematol* 2010; **2010**: 750643.

76 Tanno T, Miller JL. Iron loading and overloading due to ineffective erythropoiesis. *Adv Hematol* 2010; **2010**: 358283.

77 Peyssonnaux C, Zinkernagel AS, Schuepbach RA, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). *J Clin Invest* 2007; **117:** 1926–32.

78 Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352:** 1011–23.

79 Bregman DB, Morris D, Koch TA, He A, Goodnough LT. Hepcidin levels predict non-responsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol* 2013, **88:** 97–101.

80 Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.

81 Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085–98.

82 Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355:** 2071–84.

83 Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361:** 2019–32.

84 Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol* 2003; **122:** 394–403.

85 Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005; **23:** 5960–72.

86 Untch M, Fasching PA, Konecny GE, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel +/– darbepoetin alfa in primary breast cancer–results at the time of surgery. *Ann Oncol* 2011; **22:** 1988–98.

87 Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003; **362:** 1255–60.

88 Overgaard J, Hoff C, San Hansen H. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC): The Danish Head and Neck Cancer Group DAHANCA 10. *Eur J Cancer* 2007; **7** (suppl 5): abstract 6LB.

89 Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12·0 g/dL with erythropoietin vs above 10·0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2008; **108:** 317–25.

90 Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007; **25:** 1027–32.

91 Smith RE Jr, Aapro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Oncol* 2008; **26:** 1040–50.

92 Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009; **373:** 1532–42.

93 Hadland BK, Longmore GD. Erythroid-stimulating agents in cancer therapy: potential dangers and biologic mechanisms. *J Clin Oncol* 2009; **27:** 4217–26.

94 Swift S, Ellison AR, Kassner P, et al. Absence of functional EpoR expression in human tumor cell lines. *Blood* 2010; **115:** 4254–63.

95 Sinclair AM, Coxon A, McCaffery I, et al. Functional erythropoietin receptor is undetectable in endothelial, cardiac, neuronal, and renal cells. *Blood* 2010; **115:** 4264–72.

96 Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010; **116:** 4045–59.

97 Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; **2:** 311–16.

98 Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents: time for a reevaluation. *N Engl J Med* 2010; **362:** 189–92.

99 Goodnough LT, Shander AS. Erythropoiesis stimulating agents, blood transfusion, and the practice of medicine. *Am J Hematol* 2010; **85:** 835–37.

100 Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013; **368:** 1210–19.

101 Guyatt GH, Patterson C, Ali M, et al. Diagnosis of iron-deficiency anemia in the elderly. *Am J Med* 1990; **88:** 205–09.

102 Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004; **104:** 2263–68.

103 Raje D, Mukhtar H, Oshowo A, Ingham Clark C. What proportion of patients referred to secondary care with iron deficiency anemia have colon cancer? *Dis Colon Rectum* 2007; **50:** 1211–14.

104 Henry DH, Dahl NV, Auerbach M, Tchekmedyian S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 2007; **12:** 231–42.

105 Goodnough LT. Does plasma therapy have a role in clincial medicine? *Crit Care Med* (in press).

# Blood Transfusion 3

## Challenges in the management of the blood supply

*Lorna M Williamson, Dana V Devine*

*Lancet* 2013; 381: 1866–75

See **Editorial** page 1789

See **Comment** page 1791

This is the third in a **Series** of three papers about blood transfusion

**National Health Service Blood and Transplant, Watford, UK** (L M Williamson MD); **and Canadian Blood Services, Vancouver, BC, Canada** (D V Devine PhD)

Correspondence to: Dr Dana V Devine, Canadian Blood Services, UBC Centre for Blood Research, Vancouver, BC V6T 1Z3, Canada **dana.devine@blood.ca**

**Although blood suppliers are seeing short-term reductions in blood demand as a result of initiatives in patient blood management, modelling suggests that during the next 5–10 years, blood availability in developed countries will need to increase again to meet the demands of ageing populations. Increasing of the blood supply raises many challenges; new approaches to recruitment and retainment of future generations of blood donors will be needed, and care will be necessary to avoid taking too much blood from these donors. Integrated approaches in blood stock management between transfusion services and hospitals will be important to minimise wastage—eg, by use of supply chain solutions from industry. Cross-disciplinary systems for patient blood management need to be developed to lessen the need for transfusion—eg, by early identification and reversal of anaemia with haematinics or by reversal of the underlying cause. Personalised medicine could be applied to match donors to patients, not only with extended blood typing, but also by using genetically determined storage characteristics of blood components. Growing of red cells or platelets in large quantities from stem cells is a possibility in the future, but challenges of cost, scaling up, and reproducibility remain to be solved.**

### The challenge of matching supply with demand

Efforts in blood transfusion over the past 20 years have focused on improving viral safety and on randomised trials to establish when transfusion provides clear patient benefits. Although these efforts must be maintained, there is now also a need to develop plans to ensure that the blood supply is adequate to provide for ageing populations. In this review we aim to outline the issues facing blood suppliers in high-income countries, and we will discuss possible present and future solutions. A full discussion of the challenges facing developing countries is beyond the scope of this paper.

Health-care systems will be managing the so-called grey tsunami of ageing populations for decades to come. As a result of medical progress during the past decade, major surgery can be done without donor transfusion—eg, primary joint replacement and coronary-artery bypass grafting. However, ageing populations lead to increases in complex surgical procedures for which transfusions are still necessary, such as recurrent joint replacements and combined coronary artery and valve procedures. Success of cancer treatment in older patients and an unavoidable increase in violent trauma in young people together has an estimated increase of more than 10% in the demand for blood over the next decade (MacLennan S, National Health Service Blood and Transplant, personal communication). Another challenge is the difficulty in recruiting and retaining the next generation of blood donors. All high-income countries have to compensate for a steady decrease in regular donors with increased marketing. Issues such as iron deficiency in regular donors have caused regulators to question whether blood services are doing enough to balance donor health with the needs of patients. Finally, even if we can achieve a balance between blood supply and demand, we still have the challenge of transfusion complications in regular patients. In patients who are dependent on lifelong transfusions for thalassaemia or sickle-cell anaemia, alloimmunisation and iron overload are well recognised, but these are also increasing in older patients with acquired anaemia, such as myelodysplastic syndromes.

Therefore, all involved in vein-to-vein delivery of the blood supply need to work together to ensure that blood donation does not compromise donor wellbeing, is used only when clinically indicated, and that wastage and blood going beyond its expiration date in the supply chain is minimised. However, there is an expectation that blood will always be there when really needed; running out is not an acceptable option in countries with developed health-care systems, including during periods of extreme weather, influenza epidemics, and volcanic ash, in addition to normal fluctuations in demand. Fortunately, there are new developments in management systems for blood supply, blood component manufacturing, and donor and patient blood grouping, which can contribute to a streamlined supply chain from donor to patient. Additionally, some countries are now establishing initiatives for patient blood management, which cross health-care boundaries and aim to produce patient-care pathways that minimise the use of blood transfusions.

#### Search strategy and selection criteria

The primary source of literature was Medline, which was searched using the search terms "blood bank inventory management", "blood product production", or in the case where the work of specific investigators was sought, the author's name was used. The search focus was on papers published in the past decade with citation emphasis on articles published between 2008 and 2013 in English. Additional references were added following the initial editorial review of the manuscript at the recommendation of the referees.

These are discussed in detail in a separate report in this Series. Preparation for and response to acts of terrorism merits separate exploration, and is not discussed further in this report.

## How can we secure the donors of the future?

### Donor recruitment and retention in the digital age

Market research experts define the different generations found in the blood donor population, from the World War 2 generation, through baby boomers, to the so-called generations X, Y, and Z,[1,2] and now the so-called digital natives [3] whose smartphones are ubiquitous. Expectations of each of these groups differ substantially at all stages of contact with a blood service. Not only does the content of advertising have to vary, but also the method by which donors and blood services interact.[4,5] Donor recruitment has developed from volunteers delivering recruitment leaflets by hand, to postal contact, and now to email and text messaging. Now Facebook, Twitter, Spotify, and interactive websites are the social norms that blood services must use to enlist and retain young donors. An interactive website for donors with discussion boards, online appointment booking, and news sections could increase donor loyalty. With further development, this approach could also allow donors to complete health-check questionnaires online at home, avoiding a wasted journey if they are ineligible to donate.[6]

Donor venues might also need to be reconsidered. The present model in many countries is to reach out to rural communities, meaning blood-collection teams have to travel long distances, and this does not always result in many donors. Although this approach is seen as socially desirable, it might be difficult to continue to justify the costs. Clearly donors should not be asked to make long journeys to give blood, but blood services need to examine whether blood collection efforts can continue to be spread thinly, or should be concentrated in areas where more people are likely to donate. Another factor to be considered is the donation venue. Blood collection in village halls and local schools is possible, but limits what can be done to improve the donor experience. Fixed donor sites potentially offer more digital-age facilities, such as free WiFi and iPod docks at each bed.

### Evidence-based donor selection

Donor selection guidelines are there to protect both donors and patients from acute and long-term harm.[7] Although good epidemiological work has underpinned donor selection related to infection transmission,[8] there is scarce evidence for other exclusion criteria.[9] This absence of proper exclusion criteria for donors has resulted in highly risk-averse guidance, which has become a challenge. One good example is the upper age limit for donors, which in the UK was age 66 years. This upper age limit was extended to 70 years, but in an era where 100-year-olds run marathons,[10] even this appeared somewhat arbitrary. Therefore, in the past 10 years, after a careful review of all the evidence, both Canada and the UK abolished the upper age limit for blood donation altogether, joining the USA among other countries. Further monitoring has not found any increase in serious adverse events in these older and highly motivated donors.[11,12] The UK have started accepting donors who are treated with oral hypoglycaemic drugs (although patients on insulin treatment are not accepted, unlike in some other countries),[13,14] and extended this to patients on acceptable antihypertensive drugs. Similarly, both the US Food and Drug Administration (FDA) and the UK now accept asymptomatic donors with genetic haemochromatosis with the permission of their treating physician, provided the spirit of altruism is retained, the donor meets all other background selection criteria, and there is a back-up phlebotomy service for times when the donation cannot be taken for clinical use. Such donors are highly motivated and can provide a useful addition to the blood supply. A culture that continually updates guidance based on new evidence is now typical, and one that will resonate with the present generation of donors who are more questioning. One such review of guidelines resulted in the UK Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs recommending changing the lifetime ban from blood donation of men who have had sex with men to a 12-month deferral from last sexual contact.[15] This amendment in the guidelines was implemented in England, Scotland, and Wales in November, 2011, so far without problems. Australia has had a similar experience in changing the deferral period in men who have had sex with men, and other countries are also seeking revisions to their guidelines.[16]

### Maintaining donor health and wellbeing

Until recently, there has been little high-quality research done on the complications of blood donation, such as fainting. These complications are common in young donors; the high faint rate seen in donors aged 16 years in the USA has deterred the UK from lowering the present age limit to younger than 17 years.[17] Both Canada and the UK have recently implemented a new criterion for donor acceptance based on estimated blood volume for first-time donors aged 17–23 years, a strategy that has been effective for some US blood operators.[18] Other interventions such as drinking cold water before donation and applied muscle tension during donation have also been effective.[18] Rarely, potentially serious delayed faints can happen after the donor has left the session; their specific cause and prevention is unclear.

Long-term consequences of donation are of concern in many countries, notably the incidence of so-called haemoglobin fails and non-anaemic iron deficiency in blood donors. All donors have their haemoglobin concentrations measured before each donation, and many donors drop below the acceptance thresholds on a regular basis. Even three donations in one year can

completely use up the body's iron stores, especially in young premenopausal women with borderline iron intake. Countries vary in the acceptable haemoglobin thresholds. In Europe, the minimum thresholds were increased nearly 10 years ago from 120 g/L to 125 g/L in women and 130 g/L to 135 g/L for men, but this change was not based on systematic evidence. In both Canada and the USA, a universal haemoglobin threshold exists of 125 g/L for both men and women. Studies in the USA have shown an unexpectedly high proportion of donors with non-anaemia iron deficiency,[19] and in 2011, the FDA held a workshop to explore increasing this threshold. Another factor that varies greatly between countries is the frequency of donation, varying from 8 to 16 weeks for men, and from 10 to 16 weeks for women (table 1).

Approaches to prevent donor iron deficiency (panel 1) include the development of algorithms based on red-cell indices to predict the safest interval between donations,[20] including small trials of iron replacement[21] and a new randomised trial on the donation intervals in 50 000 donors in England (INTERVAL, ISRCTN24760606). This trial also aims to gather new information about the mental and physical consequences of non-anaemic iron deficiency, and to explore genetic factors determining susceptibility to iron deficiency. Changing the haemoglobin threshold or personalising the interval between donations are better than medicating healthy people in order for them to donate blood.

| | Men | Women |
|---|---|---|
| Austria | 8 | 10 |
| Belgium (Flanders) | 12 | 12 |
| Canada | 8 | 8 |
| Denmark | 12 | 12 |
| England | 12 | 16 |
| Estonia | 10 | 12 |
| Finland | 8 | 12 |
| France | 8 | 12 |
| Germany | 8 | 12 |
| Ireland | 10 | 10 |
| Netherlands | 10 | 16 |
| Scotland | 16 | 16 |
| Slovenia | 12 | 16 |
| Spain | 12 | 16 |
| USA | 8 | 8 |
| Wales | 12 | 16 |

Reproduced from the 2010 European Blood Alliance Survey. Data available from author on request.

***Table 1:*** **Donation intervals (weeks) in countries with national guidelines for blood donation**

***Panel 1:*** **Strategies to minimise the risk of iron deficiency in donors**

- Check haemoglobin concentration at each blood donation with conservative thresholds
- Use conservative inter-donation intervals
- Use algorithms based on blood indices to establish personalised inter-donation interval
- Use genetic and lifestyle factors to establish personalised inter-donation interval
- Give dietary advice on iron intake
- Give donors iron supplements

## Matching the donor base to patient need

A further issue in both donor and stock management is ensuring that there is always sufficient blood to meet the specific blood-type requirements of chronic transfusion recipients. All transfusions are matched for blood group (ABO) and rhesus factor D (RhD)-antigen classification, but the risk of alloimmunisation to the so-called minor blood group antigens, of which there are now known to be more than 300, increases with each transfusion, thus increasing the complexity of finding compatible blood. When genetic typing of donors and patients becomes available, it will be possible to find single nucleotide polymorphisms and other genetic variants; however, their clinical significance will have to be clearly understood because provision of compatible blood could be slowed down by trying to match for variants that are not clinically relevant. Blood services that have well characterised donor panels can deal with most patients who regularly receive blood transfusions. However, owing to differences in blood group distribution across races, and the mismatch seen in most countries between the ethnic mix of the donor and patient populations, it can be difficult to provide adequate supplies of group B red cells, especially if the patient also has many red-cell alloantibodies. This problem could lead to a default position of the use of blood group O RhD-negative blood for such patients, which is clinically safe, but puts great strain on the supply (only 7% of the UK population are O RhD negative). Additionally, minor blood group antigens such as Ss and U are distributed differently across races, so recruitment strategies are needed that engage with minority ethnic communities, patient groups, and their families. Clinical practice in patients with sickle-cell anaemia is extending the use of regular transfusions to prevent stroke.[22] Improving donor–patient matching to include minor blood groups has substantially reduced alloantibody production in patients with sickle-cell anaemia.[23] Now, the use of new DNA-based typing technologies for blood grouping,[24] coupled with sophisticated donor management strategies, have the potential to improve blood provision for these groups.

Further challenges in matching the donor base to recipients arise with the increasing use of massive transfusion protocols for trauma patients. Because it is not always possible to crossmatch the recipient, and time is critical, these patients typically receive O RhD-negative red cells and AB plasma. This practice challenges the

availability of both components for many blood providers, especially with the use of male plasma for transfusion in order to reduce the risk of transfusion-related acute lung injury (TRALI).

The restriction of which donors can be used for manufacture of particular components of blood is sometimes needed for safety reasons. For example, the USA, Canada, and the UK have mandated that fresh frozen plasma be manufactured only from male donors, to minimise the risk of TRALI caused by donor HLA antibodies. However, plasma from female donors is still acceptable for fractionation into plasma products, such as immunoglobulin, and the red cells from women are essential to the blood supply. TRALI can also be caused by the plasma in platelet concentrates, but it is not feasible to source 100% of apheresis platelets from men. Therefore, another strategy has to be used, such as testing the donors for HLA antibodies; however, this process adds to cost, complexity, and the loss of up to 15% of donors (MacLennan S, National Health Service Blood and Transplant, personal communication).

## Effect of manufacturing and storage limitation on blood supply management

In blood systems in high-income countries, transfusion is usually of specific components (eg, red cells, platelets, fresh frozen plasma) rather than whole blood, although there is renewed interest in the possibility that whole blood might be of benefit to specific patient groups.[25] Each donation is tested for bloodborne pathogens. The testing and manipulation of donations form the core processes in component manufacture. The collection and preparation of transfusion products, either by whole blood donation or apheresis procedures, generates products that have limited shelf lives, defined by the ability of storage protocols and containers to maintain the quality of the functional elements (table 2). Therefore, the resulting supply chain is highly varied, with potentially dozens of different product lines, combining donor's ABO and RhD groups and cytomegalovirus (CMV) status, the type of component, and additional manipulations such as irradiation, pathogen reduction, or washing. Management of the supply chain against this backdrop is challenging, especially when the unstable nature of cellular blood components is added to the mix.

The management of the supply of ready-to-use transfusion products has developed to minimise product wastage, with most blood systems using a "first in, first out" management system.[26] The main deviation from this practice, other than individualised products such as HLA-matched platelets, is the use of fresh red blood cells for neonatal transfusion because of concerns about the accumulation of potassium in the product supernatant during the storage period. Whether transfusion of older red blood cells is the cause of hyperkalaemia-associated cardiac events or simply associated with them has yet to be determined.[27] For some time, management of the blood supply to accommodate these patients has been a standard practice for most blood operators. Of greater concern is the increasing evidence that suggests that for some adult patients, clinical outcomes could be affected by the age of transfusion products. This concern also exists for paediatric transfusion,[28] but the only randomised clinical trial of the age of blood in neonates has shown no effect of the age of blood.[29] Little level 1 evidence exists to support this result, and retrospective studies have contradictory findings; however, within the next 2 years, several continuing clinical studies comparing fresh blood and older blood should be completed, such as the randomised controlled trial TRANSFUSE (NCT01638416), RECESS (NCT00991341), and the ABLE (ISRCTN44878718) trial of the resuscitation of critically ill patients. If these studies show that the shelf life of blood should be reduced, the level of wastage should be monitored because modelling studies suggest that, although lowering the expiration date for red blood cells is important, there is a point at which blood shortages will be inevitable.[30]

Products that have been manipulated after production typically have further restrictions on their allowable storage period, which need extra effort to ensure that products do not go to waste. Examples include irradiated red blood cells, volume-reduced products, and any product for which there is concern about sterility.

Research efforts into blood components, driven to some extent by research and development investment by the military, have begun to improve the situation. The development of synthetic additive solutions for the suspension of platelets or red cells might minimise transfusion reactions without the need to wash off the plasma. New storage systems promise extended storage life of red blood cells with good maintenance of product quality[31] and changes to the storage conditions for platelets or plasma (ie, frozen or lyophilised)[32] could similarly reduce the expiration rates and utilisation management of these components. Developments in processing technology have substantially improved the

| | Allowable storage period | Factors affecting storage |
|---|---|---|
| Red blood cell concentrate | 5–49 days depending on each country's regulations for adults and paediatric recipient | Composition of storage container, presence of additive solution, post-production manipulation such as γ-irradiation, intent of use—eg, exchange transfusion |
| Platelet concentrate | 3–7 days | Some countries allow additional days of storage up to day 7 if the product has been tested for bacteria or had pathogen-reduction technology |
| Fresh frozen plasma | 1 year (frozen)<br>24 h to 7 days (thawed) | Freezer temperature<br>Liquid *vs* frozen state |
| Cryoprecipitate | 1 year (frozen)<br>4–6 h (thawed) | Method of manufacture<br>Liquid *vs* frozen state |

*Table 2:* **Storage time for transfusion products**

consistency and reliability of components; however, the biological variation among blood donors means that manufacturing practices alone cannot optimise product quality.

Without specific attention to optimising production techniques, blood components are highly enriched but are not free of other blood elements. For example, without careful separation techniques or the use of leukoreduction filters, white blood cells might be present in any component, or platelets might be present in plasma or products of red blood cells. Some think that the contaminating platelets present in plasma products are a source of the tumour necrosis factor CD40L, which could cause adverse events in recipients;[33] however, other studies do not support a role for CD40L in transfusion reactions or TRALI.[34]

Pathogen reduction is an additional development that might have an effect on blood supply management because it is more fully implemented. Techniques typically include use of a chemical that binds to nucleic acids, coupled with a photoactivation step, and in some cases, removal of the chemical at the end of the process. Some regulatory authorities allow extended storage of platelets if they are pathogen reduced, because of the reduced risk of bacterial growth during storage, potentially offsetting some of the additional costs by a reduction in the discard rate.[35] However, these technologies cause changes in the platelet product. A recent meta-analysis of trials concluded that a common theme was reduced rises in platelet count after transfusion, although this did not result in increased bleeding.[36] If large-scale implementation was associated with increased demand for platelet transfusions to compensate, this would increase costs, and potentially restrict the overall benefit of the technology.

## Management of the blood supply stock

A nation's blood supply is distributed between the organisations that prepare blood components and the institutions that use them. In some cases, these might be one and the same. Ideally, both the producers and the users should have inventory-management systems that minimise wastage of blood products and provide immediate line of sight to the status of full blood supply. However, in some jurisdictions, producers and users do not have shared management systems to assess the blood supply. Although information technology solutions to do this exist, there are substantial hurdles, financial and otherwise, to their implementation. Interesting examples exist of integrated supply-chain management, especially where a blood operator is both the producer and the operator of the local transfusion service to patients.[37,38] Although present practices have developed empirically, blood supply systems are beginning to apply operational research to improve product ordering and inventory management.[39,40] This type of management system suggests an increasing appreciation of the alignment of many activities within a blood system to those of the traditional manufacturing sector, and recognition of the role that industrial engineering has in improving practices in the manufacturing sector.[41] The scientific literature on blood inventory management has recently been reviewed in detail.[42]

An important factor in the management of blood stocks is accurate prediction of the demand. This type of management can be restricted by insufficient information given to blood providers when a hospital changes its service provision. This can simply result in different distribution of the same number of donations in the system. However, changes to medical practice, such as approval of new chemotherapy or stem-cell transplant regimens, are more likely to affect demand for blood supply. Collection of blood that will not be used is expensive and wasteful, but undercollection of blood leads to shortages and surgery cancellations. Forecasting of blood demand tends to be based on historical patterns of use. Although this approach is generally viable, it sometimes leads to failure to see the consequences of changes in other areas of medical practice that will also affect the blood supply. An example is the rapid uptake of massive transfusion protocols from the military, which caught many hospital transfusion specialists and blood operators unaware.[43] The proposed early so-called formula replacement with high ratios of fresh frozen plasma and platelets to red cells, with the development of shock packs with many components readily available for incoming trauma victims. This approach has led to challenges with adequate collection of group O RhD-negative red cells and group AB fresh frozen plasma for some countries, although in the UK only 5% of blood group O RhD-negative units are issued as emergency.[44] To minimise wastage of fresh frozen plasma in emergency situations, in 2004, the UK allowed the extension of the post-thaw shelf life from 4 h to 24 h.[7] Other strategies to improve the accessibility of products for trauma treatment include prescreening of platelets for high titre anti-A or anti-B antibodies; ABO incompatible platelets with low titres can safely be used in trauma packs.

The best quality data for forecasting of blood demand is found in a system of vein-to-vein monitoring of blood use, such as that implemented in Oxford, UK.[45] In the absence of such a system, there are substantial challenges in combined assessment of hospital transfusion records, sales records between the blood supplier and the hospital, and the supplier's own inventory-management system. In view of the importance of appropriate blood inventory management, some countries (including the UK) have established formal national blood-stock management schemes, which feed back wastage data to hospitals and allow them to compare themselves with other management systems.[46]

Effective management of blood inventories needs to be done in a holistic manner by both the blood product provider and the hospital blood transfusion service. The

role of the transfusion service cannot be underappreciated. Decisions made by individual hospital blood banks ultimately affect the entire system's ability to meet demand, so considering the whole picture is important to the successful balance between adequate supply and minimum wastage. Within a single institution, this focus consists of having appropriately experienced personnel making decisions about ordering with the blood bank, a line of sight on all blood inventory in the hospital including other locations such as the emergency ward, and standard protocols to minimise so-called just-in-case ordering behaviour. Like blood providers, the hospital blood bank should manage stocks with strategies to avoid blood passing its expiration date or the unnecessary use of specialised products, such as CMV-negative blood.[47] Strategies such as issuing the oldest units first and implementing restocking practices of frequent small orders, rather than receiving a large stock of blood products all of a similar age are important. Implementation of electronic crossmatching has become more common and is an important way to reduce unnecessary wastage of blood.[48] This electronic system involves establishing the patient's ABO and RhD group by conventional blood typing, and screening the patient's plasma for antibodies. When blood is needed, a computer check allows the selection of suitable donations within the present supply without the need for physical crossmatching of donor and patient's blood.

Hospitals and blood providers could also work together to manage inventory through the use of return or reissue programmes that are designed to minimise expiration of blood products. Such programmes can be helped by the use of information technology solutions, such as radiofrequency identification technology.[49] Platelet concentrate products are a particular challenge for inventory management because they have a short shelf life, varying from 3 to 7 days depending on local regulatory standards. An adequate dose of platelets for an adult patient can be obtained either from one donor via an automated apheresis procedure, when the red cells are returned to the donor, or by combining buffy coats from four to six whole blood donations, then separating the platelets by centrifugation. There is no difference in the functionality of these products in preventing or treating bleeding, and blood services vary in the ratio of apheresis–whole blood platelets they produce. However, because of the small risk of transfusion transmission of variant Creutzfeldt-Jakob disease, the UK Advisory Committee on the Safety of Blood, Tissues and Organs has recommended that 80% of platelet doses are sourced from apheresis to minimise donor exposure.

The time needed to produce a platelet concentrate product and obtain all the donor test results generally means that platelets are not released for use until at least 2 days after production. The very short shelf life of plasma concentrates means that a high proportion of platelets expire before use, either at the blood supplier or in the hospital blood bank. Typical combined blood service and hospital expiration rates of plasma concentrate in countries with a 5-day shelf life can reach 25%. The short shelf life also creates inventory challenges during holiday periods. Strategies to minimise such wastage include bacterial screening of platelets combined with extension of the shelf life, and accepting that leucocyte-reduced red cells and platelets are CMV-safe, thus removing the need for a separate CMV-negative stock. In 2011, the UK Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs published a position paper stating that leucocyte-depleted red cells and platelets were adequate to protect most patients at risk of transfusion-transmitted CMV, except for pregnant women and neonates, in whom monitoring and treatment is challenging.[50] A further challenge to platelet inventory is bacterial screening, which is not normally done until 24 h after donation. Therefore, the retention of a 5-day shelf life will narrow the window of availability for tested platelet products and might increase the challenges of platelet inventory management. In England, bacterial screening has allowed the extension of the shelf life to 7 days, resulting in a reduction of expired product in blood centres from 9% to 7% (MacLennan S, National Health Service Blood and Transplant, personal communication). Additional platelet inventory can be obtained by optimising the preparation of platelet concentrates from whole blood donations, or ensuring that apheresis donors have starting platelet counts that ensure the collection of multiple products from a single procedure. On the other hand, new focus is being applied to platelet dosing as well as the need for prophylactic platelet transfusion in some patient groups.[51–53] Results of some of these studies suggest that we might be transfusing platelets more than is clinically necessary.

## Management of the patient

### Progress in the past decade

Since 1998, there have been three health service programme circulars in the UK to define a series of actions to optimise blood usage and delivery without errors to patients. Much has been achieved in the past 15 years by the combined efforts of hospital-based transfusion leaders and the UK blood services. Overall, blood use fell by nearly 16% between 2001 and 2007, and international benchmarking in 2008 put both the UK and Canada at the lower end of blood use worldwide (about 32–36 per 1000 population per year), compared with 48 per 1000 population in the USA.[54] Recent efforts to address the optimisation of blood use in the USA combined with the economic downturn have led to a substantial decrease in red cell use in the country. Despite this change, there is still much to do to ensure that every transfusion is necessary and appropriate. The notable reduction in red cell use has stalled in the UK, and national comparative audits continue to show red cell transfusion being used outside guidelines in as many as 15–20% of patients

(20–30% for platelet concentrate).[55,56] The overall fall in blood use was achieved by a 40% reduction in perioperative transfusions, but use in medicine, obstetrics, and gynaecology in the same time period did not change.[57] Therefore, a refresh of the UK approach is therefore needed.

### The concept of patient blood management

Optimum management of the patient at risk of transfusion needs a broader systems approach to the issue than is presently applied. This approach to patient management has led to the concept of patient blood management (panel 2), which has three key rules: optimisation of the blood volume and red cell mass without transfusion with the use of haematinics or substances that expand blood volume when appropriate; minimisation of blood loss with surgical technique and antifibrinolytics when needed; and optimisation of tolerance of anaemia. In the USA, the application of programmes for patient blood management is beginning to have a substantial effect on blood demand. A seminar on patient blood management, co-sponsored by the Chief Medical Officer's National Blood Transfusion Committee and NHS Blood and Transplant, was held in London in June, 2012, and several strategies were agreed on.[61]

### What resources are needed for patient blood management?

Experience in Australia and the USA confirms that for patient blood management to be successful, there has to be acceptance and input from senior leaders across the health-care system; this is because changes might be needed across the whole patient pathway, including in primary care. Within hospitals, resources are needed for 24-h availability of cell salvage and upper gastrointestinal endoscopy (for management of acute haemorrhage); and for dedicated nursing, medical, and administrative time for blood management. Production and delivery of evidence-based guidelines is also important. These guidelines have to be targeted to the right staff group because most transfusions are prescribed by junior doctors. For example, a national comparative audit of platelet usage showed a tendency for many patients to be prescribed two adult doses as routine.[62] A targeted poster campaign for junior doctors is reversing this trend. Changing care pathways to optimise transfusion use will probably work best if the pathway is being reviewed for other purposes, so opportunities should be sought to join existing pathway improvement programmes, perhaps incorporating standard methodology for clinical practice improvement.

***Panel 2:* Practice points for patient blood management[58-60]**

Although the evidence base is not complete on how to reduce blood transfusion, some general points can be made:

- Patient blood management should be built into the care pathway for each major operation or acute medical diagnosis
- Preoperative patients should have their haemoglobin concentration measured as early as possible, so that correction and investigation of iron deficiency can proceed in parallel
- Cell salvage should be available 24 h a day, as should endoscopy for investigation and potentially treatment of upper gastrointestinal haemorrhage
- A postoperative transfusion trigger should be defined; trials of liberal *vs* restrictive transfusions show no effect with a lower threshold

### Information technology challenges in patient blood management

Information technology is one of the most challenging aspects of the whole initiative. Ideally, there would be an association between hospital management and laboratory systems to link information on diagnoses and procedures in patients to blood usage. However, this approach will only happen if electronic linkage exists between the hospital patient information system and the transfusion laboratory computer, so that information on patient diagnoses and blood usage can be linked. Electronic order systems could also capture diagnostic information through a menu-driven order form, and be a method for delivering best practice guidance, perhaps through a smartphone app.

### Blood transfusion in patients with medical disorders

Management of anaemia in patients with chronic renal failure has been transformed by the use of recombinant erythropoietin and other erythropoiesis-stimulating drugs. However, recent trials have shown safety issues with these medications, such as an increase in stroke or cancer.[63,64] Data from the USA over the past 5 years show a reduction in the prescription of erythropoiesis-stimulating drugs for patients with chronic renal failure, but an increase in the use of intravenous iron and blood transfusions for this patient group.[65,66] These data might suggest both relative cost and safety concerns regarding erythropoiesis-stimulating drugs, but this shift has not been negatively associated with effect on blood stocks. A further treatment that might provide benefit is tranexamic acid.[67] The international CRASH-2 randomised controlled trial[68] in patients with trauma showed a clear reduction in mortality in the group treated with tranexamic acid, and a systematic review[67] of its use in surgery showed a 40% reduction in both mortality and transfusions.

Gastrointestinal haemorrhage has also become the focus of new research to establish the appropriate transfusion threshold for best patient outcomes. A recent randomised trial from Spain[69] showed improved survival in 421 of the 444 patients in the restrictive transfusion group (95%; threshold of 70 g/L) compared with those transfused at a threshold of 90 g/L (91%; hazard ratio 0·55,

CI 0·33–0·92). Both rebleeding and adverse events were reduced in the restrictive group, with a striking difference in transfusion rate (15% compared with 51%). A pilot trial of optimum use of blood transfusion in upper gastrointestional haemorrhage (TRIGGER, ISRCTN 85757829) is also underway in the UK.

### What further research is needed?

Panel 3 suggests performance indicators that could be used to assess patient blood management programmes. These programmes have to be underpinned by high quality research, including behavioural studies of prescribing habits. For example, the role of near-patient monitoring of coagulation in reducing fresh frozen plasma and platelet prescription is not yet fully defined, nor is the use of pragmatic preoperative intravenous iron, of which a UK trial (PREVENTT, NCT01692418) will begin shortly.

**_Panel 3:_ What performance indicators should be used in patient blood management programmes?**

It is best to choose so-called hard measures such as:

- Percentage of patients who have documented consent for transfusion, including discussion of other options
- Percentage of transfusion episodes with an appropriate pretransfusion parameter—eg, haemoglobin concentrations, and the reason for transfusion recorded in the notes
- Percentage of preoperative patients who have had anaemia screening and the results acted upon at least 14 days before surgery
- Percentage of junior doctors who have attended a transfusion education session in the past year
- Percentage of transfusion episodes with completed documentation for the order and patient observations

## Future directions

As increasing attention is paid to patient blood management and the need for clear indications for component transfusion, use of fresh frozen plasma could decrease notably because it is usually given to patients without adequate indication.[70] Even for patients who need plasma protein treatment, it is likely to be provided by more refined mixtures such as prothrombin complex concentrates, fibrinogen concentrates, and recombinant coagulation factors such as recombinant factor VIIa. In countries where these newer products are being used, some of the older products such as cryoprecipitate are hardly used anymore. Implementation of newer plasma products could come with substantial increases in cost, which might restrict their use in some jurisdictions.

In the past, all donors who were healthy enough to donate and presented no obvious risk to the recipient were able to give blood. Our practice has been to view all donors as providing similar starting material for the production of blood components. However, donor-specific characteristics have a substantial effect on the quality of components during the allowable storage period. In the future, management of the blood supply will probably involve much more sophisticated management of donors than presently. Although we do not know how this approach will affect blood-supply management practices, studies in progress in the UK (PROmPT, ISRTCN56366401) should clearly establish the association between donor characteristics and the outcome of a platelet transfusion. Recent studies have identified similarly predictive markers in healthy participants in radiolabelled platelet survival and recovery studies.[71] Recent work has suggested that donor-specific factors including sex have an effect on the storage quality of red blood cells.[72] Manufacturers of blood products already stream donors to specific kinds of donations as a strategy to minimise the risk of TRALI. For example, women with history of pregnancy cannot donate apheresis platelets in Canada and in the UK, fresh frozen plasma and platelet donors are either male or those who are negative for HLA antibodies. In the future it might be possible for donors to be characterised by their suitability for component storage, with products labelled for expiration accordingly. This approach would truly stretch our thinking around blood-supply management. As we accumulate additional information on our donor population, we could envision an intersection between enhanced donor management and the methods being developed in the application of personalised medicine. Applied correctly, this approach should lead to high-quality products that have a reduced rate of adverse transfusion events, reduced wastage, and improved overall cost-effectiveness. This approach would need more sophisticated inventory management with information technology than is presently available.

The future is also going to bring new products to the blood transfusion service. The ability to produce a transfusion product in the laboratory from different stem-cell sources has been successfully shown[73,74] and such material has been safely given to recipients.[75] Large-scale production will need solutions to challenging scientific and bioengineering problems such as blood expansion, renewal, and full red-cell maturation. Likewise, issues of consistency in quality and clinical assessment need to be solved. Although production costs remain prohibitive, these will reduce over time. To begin with, a restricted application of the technology could readily be envisioned for patients for whom compatible blood cannot be found. Expansion of production to meet the needs of wider patient groups could really change the nature of our blood supply chain in the coming decades.

In summary, blood systems exist to ensure that sufficient quality blood products are available when needed. Blood services manage products that are heavily influenced by both the availability and biological characteristics of blood donors. Strategies on how to best use blood products, and the development of processes to improve the quality of blood products will make blood transfusion a safer and more effective treatment.

**Contributors**
The authors were equal contributors to the conceptualisation and writing of this paper.

**Conflicts of interest**
LMW declares that she has no conflicts of interest. DVD receives research funding from TerumoBCT and Macopharma. She is a member of the scientific advisory committee of Fresenius-Kabi Transfusion Technologies and has received speaker fees or travel reimbursement for speaking at various conferences including the International Society for Blood Transfusion, the International Association for Biological Standards, the US FDA Blood Products Advisory Committee, Cellular Therapeutics in Trauma and Clinical Care, and the Fresenius-Kabi Advanced Course on Transfusion Technology as well as a number of visiting professorships.

**References**

1 Kolins J, Herron R. On bowling alone and donor recruitment: lessons to be learned. *Transfusion* 2003; **43:** 1634–38.
2 Ehling M, Pötzsch O. Demographic changes in Germany up to 2060—consequences for blood donation. *Transfus Med Hemother* 2010; **37:** 131–39.
3 Prensky M. Digital natives, digital immigrants part 2. Do they really think differently? *On the Horizon* 2001; **9:** 1–6.
4 Yuan S, Hoffman M, Lu Q, et al. Motivating factors and deterrents for blood donation among donors at a university campus-based collection center. *Transfusion* 2011; **51:** 2438–44.
5 France CR, France JL, Wissel ME, et al. Enhancing blood donation intentions using multimedia donor education materials. *Transfusion* 2011; **51:** 1796–801.
6 Goldman M, Ram SS, Yi Q-L, et al. The donor health assessment questionnaire: potential for format change and computer-assisted self-interviews to improve donor attention. *Transfusion* 2007; **47:** 1595–600.
7 UK Blood Transfusion and Tissue Transplantation Services. Guidelines for the UK blood transfusion services; donor selection guidelines. http://www.transfusionguidelines.org.uk (accessed Jan 25, 2013).
8 Zou S, Stramer SL, Dodd RY. Donor testing and risk: current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations. *Transfus Med Rev* 2012; **26:** 119–28.
9 Eder A. Evidence-based selection criteria to protect blood donors. *J Clin Apher* 2010; **25:** 331–37.
10 Moran L. Ginger curry and copious cups of tea: World's oldest marathon runner, 100, reveals secrets of his success. http://www.dailymail.co.uk/news/article-2032862/Ginger-curry-copious-cups-tea-Worlds-oldest-marathon-runner-100-reveals-secrets-success.html (accessed Jan 25, 2013).
11 Eder AF, Dy BA, Kennedy JM, et al. The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006. *Transfusion* 2008; **48:** 1809–19.
12 Fan W, Yi QL, Xi G, Goldman M, Germain M, O'Brien SF. The impact of increasing the upper age limit of donation on the eligible blood donor population in Canada. *Transfus Med* 2012; **22:** 395–403
13 Stainsby D, Brunskill S, Chapman CE, et al. Safety of blood donation from individuals with treated hypertension or non-insulin dependent type 2 diabetes: a systematic review. *Vox Sang* 2010; **98:** 431–40.
14 Joint Professional Advisory Committee of the UK Blood Services report 2009. Recommendations for changes to acceptance criteria for UK whole blood and component donors. http://www.transfusionguidelines.org.uk/docs/pdfs/dl_support_acceptance-criteria.pdf (accessed Jan 25, 2013).
15 UK Departments of Health advisory committee on safety of blood, tissues and organs. Donor selection criteria review 2011. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/ab/SaBTO/DH_129796 (accessed Jan 25, 2013).
16 Seed CR, Kiely P, Law M, et al. No evidence of a significantly increased risk of transfusion-transmitted human immunodeficiency virus infection in Australia subsequent to implementing a 12-month deferral for men who have sex with men. *Transfusion* 2010; **50:** 2722–30.
17 Eder AF, Hillyer CD, Dy BA, et al. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA* 2008; **299:** 2279–86.
18 Tomasulo P, Kamel H, Bravo M, James RC, Custer B. Interventions to reduce the vasovagal reaction rate in young whole blood donors. *Transfusion* 2011; **51:** 1511–21.
19 Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: the REDS II Donor Iron Status Evaluation (RISE) study. *Transfusion* 2012; **52:** 702–71.
20 Baart AM, de Kort WLAM, Atsma F, et al. Development and validation of a prediction model for low hemoglobin deferral in a large cohort of whole blood donors. *Transfusion* 2012; **52:** 2559–69.
21 Bryant BJ, Yau YY, Arceo SM, et al. Iron replacement therapy in the routine management of blood donors. *Transfusion* 2012; **52:** 1566–75.
22 Riddington C, Wang W. Blood transfusion for preventing stroke in people with sickle cell disease. *Cochrane Database Syst Rev* 2002; **1:** CD003146.
23 Lasalle-Williams M, Nuss R, Le T, et al. Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center (CME). *Transfusion* 2011; **51:** 1732–39.
24 van der Schoot CE, de Haas M, Engelfriet CP et al. Genotyping for red blood cell polymorphisms. *Vox Sang* 2009; **96:** 167–79.
25 Nessen SC, Eastridge BJ, Cronk D, et al. Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. *Transfusion* 2013; **53:** 107–13S.
26 Devine DV, Sher GD, Reesink HW, et al. International Forum: Inventory management. *Vox Sang* 2010; **98:** 295–363.
27 Vraets A, Lin Y, Callum JL. Transfusion-associated hyperkalemia. *Transf Med Rev* 2012; **25:** 184–96.
28 Karam O, Tucci M, Bateman S, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. *Crit Care* 2010; **14:** R57.
29 Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA* 2012; **308:** 1443–51.
30 Blake JT, Hardy M, Delage G, et al. Déjà-vu all over again: using simulation to evaluate the impact of shorter shelf life for red blood cells at Héma-Québec. *Transfusion* 2012; published online Nov 12. DOI:10.1111/j.1537-2995.2012.03947.x.
31 Dumont LJ, Yoshida T, AuBuchon JP. Anaerobic storage of red blood cells in a novel additive solution improves in vivo recovery. *Transfusion* 2009; **49:** 458–64.
32 Cap AP, Perkins JG. Lyophilized platelets: challenges and opportunities. *J Trauma* 2011; **70:** S59–60.
33 Bercovitz RS, Kelher MR, Khan SY, et al. The pro-inflammatory effects of platelet contamination in plasma and mitigation strategies for avoidance. *Vox Sang* 2012; **102:** 345–53.
34 Tuinman PR, Gerards MC, Jongsma G, et al. Lack of evidence of CD40 ligand involvement in transfusion-related acute lung injury. *Clin Exp Immunol* 2011; **165:** 278–84.
35 Prowse CV. Component pathogen inactivation: a critical review. *Vox Sang* 2012; published online Nov 8. DOI:10.1111/j.1423-0410.2012.01662.x.
36 Cid J, Escolar G, Lozano M. Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: results of a meta-analysis of randomized controlled trials. *Vox Sang* 2012; **103:** 322–30.
37 AuBuchon JP, Linauts S, Vaughan M, et al. Evolution in a centralized transfusion service. *Transfusion* 2011; **51:** 2750–57.
38 Yazer M. The Pittsburgh centralized transfusion model: less is more. *Transfusion* 2007; **47:** 164–68S.
39 Van Dijk N, Haijema R, van derWal J, et al. Blood platelet production: a novel approach for practical optimization. *Transfusion* 2009; **49:** 411–20.
40 deKort W, Janssen M, Kortbeek N, et al. Platelet pool inventory management: theory meets practice. *Transfusion* 2011; **51:** 2295–303.
41 Blake JT. On the use of operational research for managing platelet inventory and ordering. *Transfusion* 2009; **49:** 396–401.
42 Stranger SHW, Yates N, Wilding R, et al. Blood inventory management: hospital best practice. *Transfus Med Rev* 2012; **26:** 153–63.
43 Curry N, Davis PW. What's new in resuscitation strategies for the patient with multiple trauma? *Injury* 2012; **43:** 1021–28.

44 Foukaneli T, Grant-Casey J, Kasibante D, et al. Re-audit of the Use of group O RhD negative red cells. National Comparative Audit of Blood Transfusion Programme, NHS Blood and Transplant/Royal College of Physicians, London, 2010.

45 Murphy MF, Fraser E, Miles D, et al. How do we monitor hospital transfusion practice using an end-to-end electronic transfusion management system? *Transfusion* 2012; **52:** 2502–12.

46 Chapman J. Unlocking the essentials of effective blood inventory management. *Transfusion* 2007; **47:** 190–96S.

47 Fontaine MJ, Jurado C, Miller E, et al. Impact of cytomegalovirus (CMV) antibody reflex testing in the transfusion service on management of CMV-seronegative blood inventory. *Transfusion* 2012; **50:** 1685–89.

48 Reesink HW, Davis K, Wong J, et al. International forum: the use of the electronic (computer) crossmatch. *Vox Sang* 2013; **104:** 350–64.

49 Hohberger C, Davis R, Briggs L, et al. Applying radio-frequency identification (RFID) technology in transfusion medicine. *Biologicals* 2012; **40:** 209–13.

50 Potter M, McMahon E, Dark J, et al. Report of the Cytomegalovirus Steering Group, March 2012. https://www.gov.uk/government/publications/sabto-report-of-the-cytomegalovirus-steering-group (accessed April 29, 2013).

51 Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010; **362:** 600–13.

52 Estcourt L, Stanworth S, Doree C, et al. Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev* 2012; **5:** CD004269.

53 Stanworth S, Estcourt L Powter G, et al. The effect of a no-prophylactic versus prophylactic platelet transfusion strategy on bleeding in patients with hematological malignancies and severe thrombocytopenia (TOPPS trial): a randomized controlled, non-inferiority trial. *Blood* 2012; **120:** abstr 1.

54 Drackley A, Newbold KB, Paez A, et al. Forecasting Ontario's blood supply and demand. *Transfusion* 2012; **52:** 366–74.

55 Hearnshaw SA, Logan RF, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; **60:** 1327–35.

56 Boralessa H, Goldhill DR, Tucker K, Mortimer AJ, Grant-Casey J. National comparative audit of blood use in elective primary unilateral total hip replacement surgery in the UK. *Ann R Coll Surg Engl* 2009; **91:** 599–605.

57 Tinegate H, Chattree S, Iqbal A, et al. Ten-year pattern of red blood cell use in the north of England. *Transfusion* 2012; published online July 15. DOI:10.1111/j.1537-2995.2012.03782.x.

58 Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of perioperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth* 2011; **106:** 13–22.

59 Hebert PC, Wells G, Blajchman MA, et al. A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340:** 409–17.

60 Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365:** 2453–62.

61 Department of Health, the National Blood Transfusion Committee, NHS Blood and Transplant. Patient Blood Management: the future of blood transfusion conference. June 18, 2012. http://www.transfusionguidelines.org/Index.aspx?Publication=NTC&Section=27&pageid=7729 (accessed Jan 25, 2013).

62 Estcourt LJ, Birchall J, Lowe D, et al. Platelet transfusions in haematology patients: are we using them appropriately? *Vox Sang* 2012; **103:** 284–93.

63 Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361:** 2019–32.

64 Locatelli F, Aljama P, Canaud B, et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to reduce cardiovascular events with Aranesp therapy (TREAT) study. *Nephrol Dial Transplant* 2010; **25:** 2846–50.

65 Pisoni RL, Fuller DS, Bieber BA, et al. The DOPPS Practice Monitor for US dialysis care: trends through August 2011. *Am J Kidney Dis* 2012; **60:** 160–65.

66 Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 annual data report. *Am J Kidney Dis* 2010; **55:** S1–420.

67 Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344:** 3054.

68 CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011; **343:** d3795.

69 Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl JMed* 2013; **368:** 11–21.

70 Pinkerton PH, Callum JL. Rationalizing the clinical use of frozen plasma.*CMAJ* 2010; **182:** 1019–20.

71 Schubert P, Culibrk B, Karwal S, et al. Optimization of platelet concentrate quality: application of proteomic technologies to donor management *J Proteomics* 2012; **76:** 329–36.

72 Raval JS, Waters JH, Seltsam A, et al. Menopausal status affects the susceptibility of stored RBCs to mechanical stress. *Vox Sang* 2011; **100:** 418–21.

73 Mountford J, Olivier E, Turner M. Prospects for the manufacture of red cells for transfusion. *Br J Haematol* 2010; **149:** 22–34.

74 Reems JA, Pineault N, Sun S. In vitro megakaryocyte production and platelet biogenesis: state of the art. *Transfus Med Rev* 2010; **24:** 33–43.

75 Giarratana MC, Rouard H, Dumont A, et al. Proof of principle for transfusion of in vitro-generated red blood cells. *Blood* 2011; **118:** 5071–79.