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Annotation

HOMOLOGOUS BLOOD TRANSFUSION: THE RISKS AND ALTERNATIVES

There are currently draft proposals within the British Committee for Standards in Haematology (BCSH) which may recommend that patients give formal consent for blood transfusion, as is already the case in several European countries, including France, Germany, Norway and Italy. It is therefore timely to review the risks, both perceived and real, of homologous donated blood in the U.K., and the methods by which exposure to donor blood might be avoided. In certain States of the U.S.A. it is a legal requirement to offer options to donor blood, and in the U.S.A. as a whole autologous donations account for 6% of all donations collected, with 'directed' donations for friends or relatives providing a further 3% (Devine *et al*, 1992). In the U.K., autologous donations amount to no more than a fraction of 1% of all blood collected, and current guidelines do not recommend directed donations at all, except under certain very specific circumstances (BCSH Blood Transfusion Task Force, 1993).

Both medical and public opinion would probably rank HIV transmission as the prime complication of donor blood, but in fact the single biggest cause of mortality remains transfusion of the wrong pack of blood, potentially resulting in major ABO incompatibility. Such incidents arise either from mislabelling of the crossmatch sample, or confusion of two patients at the time of transfusion. There is no formal reporting system for either major transfusion errors or 'near-miss' events, but a recent survey suggests that the risk of such an incident is approximately 1/30 000 units transfused, with at least six fatalities in the U.K. in the last 2 years (McClelland & Phillips, 1994). Whether such events will be less frequent in the context of autologous transfusion remains to be seen.

Viral hazards of donor blood

The viral risks of transfusion of blood components (red cells, fresh frozen plasma, cryoprecipitate and platelets) from U.K. voluntary blood donations must be differentiated from those of fractionated plasma products such as factor VIII which are now subjected to effective methods for the elimination of the most important blood-borne viruses, namely HIV 1 + 2, hepatitis B, and hepatitis C (HCV). None of the blood components listed above is currently subjected to any form of viricidal treatment, although solvent-detergent fresh frozen plasma is available in Europe, and may begin clinical trial in the U.K. this year. Viral safety depends therefore on careful donor selection and thorough viral testing. The importance of donor selection should not be underestimated. Once the link between HIV and blood transfusion had become apparent in the U.S.A. in the early 1980s, exclusion of 'high-risk' individuals from donor panels had a striking impact on the incidence of transfusion-transmitted HIV infection, even before screening tests for blood donations became available. Since donor testing for HIV was introduced in the U.K. in October 1985 there has been only one documented case of HIV transmission by blood transfusion, in over 16 million donations collected (Crawford *et al*, 1987).

Transmission of hepatitis B and HCV by transfusion remains numerically more important than that of HIV. There are probably 10–100 cases of transfusion-transmitted hepatitis B annually in the U.K. (J. Barbara, personal communication), equating to a risk of 1 in 20–200 000. A proportion of transmissions might be preventable by additional testing of donors for antibodies to the core protein of the virus in addition to the standard surface antigen test, but this is not likely to be introduced in the U.K. in the foreseeable future. The current risk of acquiring HCV via transfusion is yet higher, perhaps 1 in 5–10 000 (Carson *et al*, 1992).

Screening of blood donations for HCV has been in place in the U.K. only since 1991. Second- and third-generation tests with greater sensitivity are now available, suggesting that >90% of post-transfusion hepatitis might currently be eliminated. Bearing in mind that recipients of 50% of all blood transfused have died of their underlying disease by 1 year, the risks not only of disease transmission but of clinical sequelae become relevant. For HIV, serious clinical consequences are usually apparent within a few years of seroconversion, and in the vast majority of anti-HIV positive individuals eventually. On the other hand, HCV may remain asymptomatic, or follow an extremely slow progression to significant liver disease (chronic active hepatitis and cirrhosis) in only a proportion of infected individuals over 10–20 years (Seeff *et al*, 1992). Thus efforts taken to avoid exposure to donor blood in an individual patient must be tempered by the patient's age and underlying condition.

Immunomodulatory effects of transfusion

Unlike the risks of viral transmission, the immunomodulatory effects of transfusion have been tantalizingly difficult to establish, although considerable background evidence suggests that such an effect is likely. Ever since the demonstration that pre-transplant transfusions aided renal allograft survival (Woodruff & van Rood, 1983; Opelz & Terasaki, 1976) there have been animal (Waymack *et al*, 1986) and human (Fernandez *et al*, 1992b; Jensen *et al*,

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1992) studies demonstrating suppression of a variety of lymphocyte subsets and of natural killer cells following transfusion. The search for clinical sequelae of such phenomena continues, and has to date focussed on post-operative infection and immune surveillance of tumours, particularly carcinomas of colon and rectum. In orthopaedic surgery, homologous transfusion has been identified as a significant independent predictor of post-operative infection (Triulzi *et al*, 1992; Fernandez *et al*, 1992a). In addition, a prospective randomized study comparing autologous with homologous donation in colorectal cancer surgery found significantly fewer post-operative infections in the autologous group (Heiss *et al*, 1993).

To address the question of colorectal cancer recurrence following transfusion, a number of observational studies have been carried out and recently subjected to thorough statistical scrutiny looking for confounding variables which might independently influence both tumour recurrence and the need for perioperative transfusion (reviewed in Vamvakas & Moore, 1993). Of the 25 retrospective studies analysed, 15 showed a deleterious effect of transfusion, nine detected no influence of transfusion, whereas only one showed benefit. Initial analysis of the 15 studies showing a transfusion effect appeared to suggest that tumour recurrence could be up to 37% greater in transfusion recipients. However, on more detailed scrutiny, this could be explained almost entirely by variables not considered by the investigators. Two prospective studies examining the effect of transfusion on colorectal cancer recurrence have given conflicting results (Tartter, 1992; Crowson *et al*, 1989), and two further randomized trials comparing homologous and autologous transfusion again gave different outcomes (Heiss *et al*, 1992; Busch *et al*, 1993). Small studies have also found an association between transfusion and recurrence of other tumours such as those of lung and kidney (Blumberg *et al*, 1990), but again causation is far from proven. Even if a deleterious effect of transfusion of homologous blood is proved, the practical difficulties of achieving benefit by autologous transfusion for large numbers of patients should not be underestimated (Harrison *et al*, 1992), because anaemia, certain cardio-respiratory problems and urgency of surgery will all preclude pre-operative autologous donation.

On the basis that any immunosuppressive effect of transfusion is likely to involve donor lymphocytes, two studies have examined the effect of blood depleted of leucocytes by filtration on both post-operative infection and colonic cancer recurrence. The first study found fewer post-operative infections in patients receiving leucocyte and plasma-depleted blood during surgery for colorectal cancer (Jensen *et al*, 1992), but as the control group received whole blood, an independent effect of plasma could not be excluded. The second study of over 800 colorectal cancer patients (A. Brand, personal communication) compared both post-operative infections and tumour recurrence in patients receiving red cells which were either leucocyte depleted ($<10^6$ leucocytes/unit) or buffy coat depleted ($<10^9$ leucocytes/unit). Transfusion of either product correlated highly with post-operative infection but no benefit was conferred by greater leucocyte removal. Tumour recurrence was no more frequent in transfused patients, but disease-free and overall survival were shorter. However, these observations could be explained entirely by independent risk factors for tumour recurrence. As with post-operative infection, greater leucocyte depletion of transfusions offered no advantage. These results suggest that any transfusion effect on immune function may be subtle, and as yet ill understood.

Avoidance of homologous blood

For the clinician and patient wishing to avoid donor blood, a wide range of options exist either singly or in combination (Table I), although their availability in the U.K. is patchy.

Table I. Avoiding homologous blood.

Alternative means of volume expansion
Crystalloids
Colloids
Autologous red cells
Pre-operative deposit
Peri-operative haemodilution
Intra- or post-operative cell salvage
Pharmacological means to reduce blood loss
Aprotinin
DDAVP
Scrupulous surgical technique
Recombinant human erythropoietin
Synthetic oxygen carriage
Haemoglobin solutions
Perfluorocarbons

Studies in patients who refuse transfusion for religious reasons have demonstrated the scope of techniques to avoid homologous blood exposure (Atabek *et al*, 1992; Carson *et al*, 1988). The most obvious strategy in elective surgery or other moderate blood loss (500–1000 ml) would be to avoid red cells altogether, maintaining blood volume and cardiac output with safe colloid preparations. In such circumstances a haemoglobin as low as 8 g/dl appeared to have no deleterious effect on survival, provided there was good cardiac function (Carson *et al*, 1988). The Consensus Conference on Perioperative Red Cell Transfusion held at the U.S. National Institutes of Health in 1988 failed to reach a conclusion on the need to transfuse patients with haemoglobin values between 7 and 10 g/dl, but recommended abandoning the '10/30' (Hb/Hct) rule in favour of clinical judgement (National Institutes of Health, 1989). The consensus Conference on Red Cell Transfusion recently held in the U.K. has shed further light in this grey area. Unnecessary transfusions remain a problem in both orthopaedic (Goodnough *et al*, 1992) and colorectal (Hallissey *et al*, 1992) surgery, and may account for up to 30% of peri-operative transfusion. Correction of this may require considerable effort, such as involvement of senior surgical or anaesthetic staff in the decision to transfuse patients post-operatively. This would be a far cry from the routine post-operative

'top-ups' with which we are all too familiar. The establishment of clinical audit via hospital transfusion committees could have considerable benefit in this area.

Where transfusion is unavoidable, simple manufacturing steps can reduce donor exposure considerably, such as production of fresh frozen plasma by apheresis. Reduction of donor exposure is best seen in premature neonates, who are one of the most intensively transfused group of patients in any hospital. Splitting red cell donations into multiple small volumes allows dedication of a single donation for multiple top-ups to the same infant over a 5-week period.

Pre-operative autologous transfusion

Of all the means to avoid donor exposure, pre-operative donation of 2–4 units of red cells for autologous transfusion has received most attention. Variations of this have been advocated, but long-term storage of cryopreserved autologous cells 'just in case' is best reserved for those few patients in whom multiple or rare red cell antibodies preclude transfusion of donor blood. Glycerol has generally been used as the cryoprotectant, but has to be thoroughly washed off the cells after thawing. An alternative cryoprotectant, requiring no washing steps, is hydroxylethyl starch (HES), which allows either long-term red cell storage in the vapour phase of liquid nitrogen, or shorter-term storage at −90°C (Thomas, 1990). Directed donations from family or friends of the patient are not recommended (BCSH Blood Transfusion Task Force, 1993), offering no greater and perhaps less safety than donor blood given without coercion. Absolute contraindications to directed donations include donation from a man to his female partner where future pregnancies are planned, and from a potential bone marrow donor to the patient prior to the transplant (Page, 1988). Where family donations are unavoidable, e.g. from mother to child in neonatal alloimmune thrombocytopenia, blood components must be irradiated to prevent the increased risk of transfusion-associated graft-versus-host disease.

Early restrictions on patient selection for autologous donation are gradually being relaxed as experience is gained, and the newly revised U.K. Guidelines list only active bacterial infection, unstable angina, aortic stenosis and uncontrolled hypertension as absolute contraindications (BCSH Blood Transfusion Task Force, 1993). Provided oral iron supplements can be tolerated, and a haemoglobin of >10 g/dl maintained, autologous donation is usually well tolerated, even in the elderly. A new register of serious adverse effects to autologous donation, to be maintained by the Royal College of Physicians of Edinburgh, will allow monitoring of this. Elective orthopaedic surgery is a good example of an area in which autologous pre-deposit transfusion has found a place, but in the NHS late cancellation of surgery can lead to wastage. In such circumstances, autologous units can be returned to the donor and new donations taken to extend the shelf-life, but this greatly adds to the inconvenience for the patient. Children as young as 7 years have successfully pre-deposited appropriate volumes of blood (DePalma & Luban, 1990) prior to spinal surgery. Pregnancy *per se* is not a contra-indication to autologous donation, but it is only an indication if the patient has a particularly high chance of requiring transfusion at delivery, since currently <3% of births are associated with maternal transfusion (Kruskall, 1990). The haemodynamic changes of blood donation are well tolerated in pregnancy, provided care is taken to avoid caval compression by the uterus by bleeding the patient in the lateral position (Kruskall, 1990). Currently, a number of autologous programmes are in place in the U.K., with Blood Transfusion Centre involvement in collection, testing and labelling (Howard *et al*, 1992).

A number of areas of controversy surround pre-operative autologous donation. Firstly, it is currently required that each donation be tested for the same range of viral markers as homologous donations, even although 'crossing over' of unused units into blood bank stock is rightly disallowed. Viral testing increases the costs, and creates dilemmas if confirmed positive results are obtained. Hospital patients have a higher prevalence of markers of HCV infection than new blood donors (Allain, personal communication), so such an occurrence may not be infrequent. Current U.K. Guidelines recommend that autologous units testing positive for markers of HIV, hepatitis B or HCV be discarded (BCSH Blood Transfusion Task Force, 1993). In the U.S.A., however, virologically positive blood may still be used, at the clinician's discretion, provided that clear separation from donor stock can be achieved (American Association of Blood Banks, 1993). Secondly, some studies have demonstrated that pre-operative collections can be increased by the use of recombinant human erythropoietin (rhEPO), and that the fall in Hb associated with pre-deposit donation is prevented (Beris *et al*, 1993; Goodnough *et al*, 1989; Kyo *et al*, 1992). However, only one of these trials reported a reduction in homologous blood use in the rhEPO group, and it appears that administration of rhEPO in the context of autologous transfusion can only be justified if 5 or 6 units of blood are to be collected (Beris *et al*, 1993; Goodnough *et al*, 1989). A later study also failed to demonstrate any clinical benefit of rhEPO to non-anaemic patients undergoing pre-deposit for orthopaedic procedures (Goodnough *et al*, 1994). These studies suggest that the role of rhEPO in the context of pre-deposit autologous transfusion is likely to remain limited. In view of the possible increase in whole blood viscosity by rhEPO (Spivak, 1994) the wisdom of this approach to autologous donation has been questioned (Gillon *et al*, 1991).

The recent report of sepsis in a patient due to transfusion of an autologous unit containing the cryophilic bacterium *Yersinia enterocolitica* is a reminder that this recognized complication of homologous transfusion may also accompany autologous donations (Richards *et al*, 1992). Care must be taken to audit the appropriate use of autologous units, in view of the observed tendency to return autologous blood to the patient 'just because it's there' (Goodnough *et al*, 1992). Finally, in these days of increased interest in health-care economics, the cost-effectiveness of pre-deposit autologous transfusion has been questioned, even in the U.S.A. Cost-effective analyses of pre-deposit autologous donation in coronary artery and orthopaedic surgery have been performed, using the standard quality-adjusted life

expectancy in years (QALY) as an outcome measure. The average (as opposed to individual) benefit was <0·001 QALY (<0·3 d/patient), while the cost effectiveness of the procedure was calculated at between $100 000 and $1 000 000 per QALY (AuBuchon & Birkmeyer, 1994). Depending on the methods used to cost autologous donation, it has been claimed to be cheaper, equivalent, and more costly than donor blood. It is certainly more labour intensive to collect and handle autologous donations, although, unlike homologous donations, they are rarely processed to components. Given the low risk of viral transmission, therefore, the only pressing economic arguments for widespread autologous provision would be either if a significant reduction in tumour recurrence could be demonstrated, or if post-operative antibiotic usage or duration of hospital stay could be shown to be consistently reduced.

Perioperative blood sparing

Manoeuvres which can be undertaken around the time of surgery are more likely to prove cost-effective, because they demand less patient and staff time and are not affected by postponement of surgery. Normovolaemic haemodilution, which is currently underutilized, involves removal of 500–1000 ml of blood during induction of anaesthesia with replacement by crystalloid to a haematocrit of 25–30% (Takaori, 1991). Surgery is well tolerated at this haematocrit, provided cardiorespiratory function is not compromised, and oxygen delivery to the tissues may well be improved by the reduction in blood viscosity. Since the collected blood remains in theatre to be returned at the end of surgery, if needed, there is no need for viral testing and the risk of blood return to the wrong patient is minimized. In a randomized study of patients undergoing prostatectomy, perioperative haemodilution was as effective in preventing homologous transfusion as pre-deposit of 2 units of autologous blood (Ness *et al*, 1991), with no difference in perioperative morbidity. A slightly different procedure is followed in hypervolaemic haemodilution, where crystalloid and colloid are infused without concomitant blood withdrawal (Trouwborst *et al*, 1990), but this has not been formally compared either to pre-deposit or to normovalemic haemodilution.

Intra-operative salvage and recycling of blood was originally used in very high volume losses into body cavities, as occurred in the early days of liver transplantation (Williamson *et al*, 1989). Combined with a rapid infusion system, up to 5 l/h of washed salvaged red cells can be returned to the patient. As concomitant infusion of colloid, clotting factors (as fresh frozen plasma) and platelets is required, some exposure to donor blood components is inevitable. A range of cell salvage equipment is now available, and has been successfully used in aortic (Clifford *et al*, 1987) and orthopaedic (Goulet *et al*, 1989; Wilson, 1989) surgery, with savings in homologous blood of 42–70%. Perhaps surprisingly, a randomized trial of intra-operative salvage in coronary artery surgery demonstrated median savings of only one homologous unit/patient (Bell *et al*, 1992), although salvage patients had higher post-operative haemoglobin values, suggesting a degree of over-transfusion. An extension of intra-operative salvage is post-operative recycling, where blood from wound drains can be re-infused intravenously, with appropriate filtration of cellular debris. This has successfully reduced homologous blood usage in orthopaedic surgery (Heddle *et al*, 1992), but the finding of febrile reactions to such blood, along with positive bacterial culture (Heddle *et al*, 1992) and particulate matter in some filtered units (Robbins *et al*, 1992), suggests that clinical complications of this technique should be carefully monitored.

Drugs which reduce blood loss

Use of drugs such as desmopressin (DDAVP) and aprotinin to reduce blood loss has been investigated in cardiac bypass and liver transplant surgery. The rationale for their use is based on an understanding of haemostasis and its defects in the surgical setting (Hunt, 1991; Murphy *et al*, 1993), although knowledge in this area is far from complete. Surgery is associated with rapid activation of fibrinolysis via tissue plasminogen activator (t-PA) and the contact factors pre-kallikrein and factor XII. Particularly high levels of t-PA have been noted during the anhepatic phase of liver transplantation (Dzik *et al*, 1988). In addition to the fibrinolytic changes, cardiac surgery has been associated with multiple defects of platelet function, including loss of the glycoprotein Ib/IX complex which carries the von Willebrand factor receptor. An alternative theory, however, is that the platelet defect can entirely be accounted for by unavailability of platelet agonists (Kestin *et al*, 1993).

DDAVP increases plasma concentrations of von Willebrand factor, but has been disappointing as a blood sparing agent in routine cardiac surgery (Hackmann *et al*, 1989). It has been suggested that desmopressin might be of value where excessive bleeding (>1100 ml) occurs after cardiac surgery (Cattaneo & Mannucci, 1993), but unfortunately there is no simple laboratory parameter which will predict major and unexpected surgical blood loss. In contrast, the serine protease inhibitor aprotinin has achieved dramatic reductions in surgical 'oozing' in cardiac surgery, reflected in reduced transfusion requirements and shorter operation times (Hunt, 1991). Even in repeat cardiac procedures, blood loss has been reduced from 1500 to 300 ml (Royston *et al*, 1987), whereas in liver transplantation the increased blood demand usually seen in cirrhotic patients has been prevented (Smith *et al*, 1993). The mode of action of aprotinin is probably at least partially via inhibition of plasmin and activated protein C (Hunt, 1991), and perhaps also by prevention of proteolytic cleavage of platelet glycoprotein Ib, although the evidence for a platelet effect has been challenged (Orchard *et al*, 1993).

Recombinant human erythropoietin (rhEPO)

The use of rhEPO has revolutionized the management of the anaemia of chronic renal failure. Patients awaiting renal transplant can now live transfusion-free lives if maintained on regular rhEPO (Winearls *et al*, 1986; Eschbach *et al*, 1987) without the risks of development of lymphocytotoxic antibodies which restricts the selection of donor kidneys. Side-effects such as fits and hypertension can be minimized

by careful increase of the dose to achieve a gradual rise in haemoglobin (Sundal *et al*, 1991). Its high cost may limit its more widespread use in the U.K., but good effect has been seen in the anaemia accompanying zidovudine therapy of AIDS (Fischel *et al*, 1990), rheumatoid arthritis (Pincus *et al*, 1990) and myelofibrosis (Bessho *et al*, 1990). The bone marrow of premature neonates has also been shown to be responsive to rhEPO in culture, with responses of erythroid colony-forming-units at similar rhEPO concentrations to that of adult marrow (Rhondeau *et al*, 1988). Clinical studies of its use in premature neonates are beginning to show promise. A dose of rhEPO of 100 units/kg twice weekly failed to produce a rise in haematocrit, and had a minimal effect on transfusion requirements (Shannon *et al*, 1991), but in a randomized study of 200 units/kg on alternate days for 10 d symptoms of anaemia resolved, even though the rise in haematocrit was on average only 3% (Ohis & Christensen, 1991). Finally, a multicentre European trial of 750 IU/kg/week in infants weighing 750–1500 g showed significantly reduced transfusion need with satisfactory maintenance of haematocrit in the rhEPO group (Maier *et al*, 1994). Finally, rhEPO has been used in surgical patients in the absence of autologous collection. One randomized three-arm study of elective hip arthroplasty compared placebo, 300 units/kg rhEPO for 14 d, starting 10 d before surgery, and the same dose for 9 d only (Canadian Orthopedic Perioperative Erythropoietin Study Group, 1993). Haemoglobins of <8 g/dl and transfusions were significantly more common in the placebo group, although deep venous thromboses were slightly more frequent in both rhEPO groups than in control patients. It is far from clear what the long-term role of rhEPO will be in the surgical setting, but there is clearly great potential for patients in whom transfusion is undesirable.

Artificial blood

The prospect of 'artificial blood', which in reality means a synthetic means of providing oxygen carriage, has been on the horizon for some years, but at the moment seems little nearer clinical use. The two main contenders are haemoglobin, either encapsulated or in solution, and fluorocarbons. Haemoglobin solutions have traditionally been produced from outdated blood, and have therefore depended on donor supply. In addition, non-cellular haemoglobin displays a number of undesirable characteristics. The molecule tends to dissociate from the tetrameric to the $\alpha\beta$ dimeric form, which is rapidly cleared by the kidney, causing renal damage. A cross-linker such as pyridoxal phosphate is therefore necessary, plus a polymerizing agent, e.g. gluteraldehyde, to produce an isotonic solution. An additional factor is that the lack of 2,3-bisphosphoglycerate causes the oxygen dissociation curve to move to the left, impairing oxygen off-loading to the tissues. The main problems facing manufacturers of such solutions are therefore production of a solution with an ideal P_{50}, prevention of spontaneous oxidation to methaemoglobin, and prevention of immediate adverse reactions, which may relate to either trace amounts of polymerizing chemicals or to complement activation. Molecular engineering now allows synthesis of human haemoglobin in *E. coli* potentially solving problems of both supply and biochemical characteristics. An elegant remodelling of the molecule has been achieved to produce a recombinant haemoglobin with fusion of the two alpha units, substantially increasing the half-life, and an asparagine → lysine mutation in position 108 of the β chain to reduce oxygen affinity (Looker *et al*, 1992). This paves the way for haemoglobin therapy completely independent of human supply, provided that manufacture of products sufficiently pure of bacterial proteins can be achieved. Liposomal haemoglobin seems an attractive alternative, but reticuloendothelial uptake with possible blockade remains a problem.

Perfluorocarbons dissolve oxygen, so function only in high concentrations of ambient oxygen (Lowe, 1991). For clinical use, they must be emulsified, rendered isotonic and mixed with surfactant. Fluosol-DA, the most widely tested solution, is a mixture of two perfluorocarbons. Its limitations include low oxygen-carrying capacity and severe reactions in some patients. Clinical studies have given disappointing results, with high mortality in treated patients (Gould *et al*, 1986; Spence *et al*, 1990). The use of perfluorocarbons is now currently restricted to local perfusion during coronary balloon angioplasty (Kent *et al*, 1990) and for increasing radiosensitivity of tumours, but a new generation of fluorocarbons has been produced and awaits clinical evaluation. However, clinicians will have to give manufacturers clear guidance on what specifications any 'blood substitute' must have. This can only follow from a rational set of clinical objectives, not so far developed in this area.

Conclusion

It is likely that the next 5 years will see considerable reappraisal of the way homologous blood is used in clinical practice. Peri-operative techniques probably offer the widest scope for 'blood sparing', and a role will emerge for both recombinant erythropoietin and haemoglobin. A multidisciplinary approach, involving haematologists, transfusion specialists, anaesthetists, surgeons and perfusionists, will be required to ensure that such new developments will be used rationally and cost-effectively.

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