

Guidelines for policies on Alternatives to Allogeneic Blood Transfusion

1. Predeposit Autologous Blood Donation and Transfusion.

British Committee for Standards in Haematology

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1. Predeposit Autologous Blood Donation and Transfusion.

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Summary

This is the first of a series of newly prepared guidelines on alternatives to allogeneic blood transfusion. Further guidelines including the use of cell salvage and of pharmacological approaches to blood conservation will be published in due course.

Decades of clinical application demonstrate that it is quite feasible to auto-transfuse blood which has been collected and stored for an interval of up to six weeks in standard storage media, and that up to three standard collection volumes (approximately 500 ml) can be collected from normal sized adults (over 50Kg) during that interval. Furthermore, systems have been developed to reduce risk to participants, and to boost haemoglobin production during and after the procedure. However, such “Preoperative Autologous Donations” (PAD) are not without risk, are of low clinical efficacy and are poorly cost-effective for the vast majority of patients in the UK. These Guidelines update those previously issued by the BCSH and do not recommend the practice and use of PAD unless the clinical circumstances are exceptional. They also give an update on the legal regulatory circumstances pertaining to the UK following recent European Directives.

Methods

Searches on Medline and PubMed, using the following terms; autologous, blood transfusion, pre-operative, pre-deposit, EPO, iron, cardiac surgery, elderly, children, orthopaedics, directive, regulations. The recent European and UK legislation has also been scrutinised.

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research and are set out in the following tables: *Statements of evidence*

Ia	Evidence obtained from meta-analysis of randomized controlled trials.
Ib	Evidence obtained from at least one randomized controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomization.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.
<i>Grades of recommendations</i>	
A	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (evidence levels Ia, Ib)
B	Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. (evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (evidence level IV)

Scope and purpose:

These guidelines comment on and update the policies for predeposit autologous blood donation and subsequent transfusion of the stored component described in the previous BCSH Guideline (1993). The term Predeposit Autologous Blood Donation (PABD, PAD) refers to the collection and subsequent storage of blood in a manner similar to the collection and storage of blood from healthy unremunerated volunteers donating for general use except that the person from whom the blood is collected is intended also to be the recipient, the whole process being planned for the clinical benefit of that person by covering an expected loss of a significant amount of blood resulting from, for example, elective surgery. Although the term 'donation' in the autologous setting runs counter to logic, its use for this purpose has been widely accepted and will be continued where appropriate in the rest of this Guideline, usually in the acronym PAD.

The 1993 Guidelines referred specifically to blood "which is stored at 4°C in CPD A1 for up to 35 days or in an optimal additive solution up to 42 days", and covered many practical aspects including model proformas for

- obtaining referral letters
- obtaining consent
- labelling the packs
- collecting the blood. This included
 - timing (minimum intervals of a week and the ultimate collection four days before surgery)
 - volume (no more than 12% estimated blood volume at each collection)
 - oral iron therapy for all PAD patients

They also

- stressed that PAD was only suitable for a minority of patients, principally those who could be expected to benefit from standard transfusion policies directed by 'Maximum Surgical Blood Ordering Schedule (MSBOS)'
- recommended that application should accord to a Standard Operating Procedure, which would include an assessment of fitness to donate
- advised that patients infected with hepatitis B, hepatitis C or HIV/AIDS be excluded
- recommended minimum haemoglobin concentrations (Hb) of 110g/l blood for men and women
- stated that the use of erythropoietin to encourage haemopoiesis 'remains unclear'
- referred to PAD in children, smaller adults and pregnant women
- recommended cardiological advice for patients with heart disease or receiving beta blockers or angiotensin converting enzyme (ACE) inhibitors
- recommended no PAD for patients with a history of epilepsy
- stressed that other ways of avoiding allogeneic transfusion should always be considered
- as an aside, specifically did not recommend directed donation.

The 1993 Guidelines were prepared at a time when PAD was generally favourably and even enthusiastically undertaken in some quarters. For example, Isbister in 1991 compared allogeneic – then often called 'homologous' – transfusion to bank loans which were easier to get, while PAD was analogous to the implicitly more worthy but

harder work of saving money up for oneself. In 1994, Hardy *et al*, who advocated the use of erythropoietin in PAD, stated that PAD ‘must become an integral part of strategy for centres where cardiac surgery is performed’. However, more recent opinion has been somewhat more guarded. Regulations regarding PAD *collection* are now covered by Directives from the European Commission and the UK Blood Safety Regulations 2005, which are legally binding. The *clinical use* of PAD blood is not so regulated, being subject more to professional judgement as to clinical need: this will also be covered in these Guidelines, particularly where practice has changed and parts of which are now legally regulated.

Stakeholder Involvement

These Guidelines, which should be shared with patients who request or enquire after this form of transfusion therapy, are aimed at and have been approved by

- Clinicians who may wish to undertake this form of therapy,
- Senior representatives of Blood Establishments in the UK and
- Hospital blood banks considering applying for valid appropriate authorisation.

Aspects covered

These Guidelines deal almost entirely with the collection, testing, processing and use of whole blood collected by procedures which closely follow those for standard allogeneic blood collection, and stored for up to 35 days prior to autologous transfusion. Red cell and platelet components collected by apheresis are referred to briefly.

The Guidelines are presented in three Parts

- Part 1; UK Legislation and Relevant European Directives
- Part 2: Literature review and current clinical practice
- Part 3: Recommendations based on an analysis of the above

Part 1. UK Legislation and Relevant European Directives; a summary of the main Regulations covering autologous donations applicable to the UK in 2006.

The UK Blood Safety Regulations 2005, which came into effect on November 8th 2005, transpose the European Commission Directive 2004/33/EC into UK law. This Directive in turn implements Directive 2002/98/EC.

Two further technical Directives were adopted by the European Commission on 30 September 2005 and, according to the Medicines and Healthcare Regulatory Authority (MHRA, website accessed April 2006), following public consultation will be transposed into UK legislation. These are:

- Directive 2005/61/EC regarding traceability requirements and notification of serious adverse reactions and events;
- Directive 2005/62/EC regarding Community standards and specifications relating to a quality system for blood establishments.

The Regulations and the Directives describe the legal requirements for collecting, processing, testing, transporting and storing blood components. They legislate principally for allogeneic transfusion but there are several references to “autologous donation” and “autologous transfusion”. Although they do not mention the terms ‘pre-operative’, ‘PAD’ or ‘PABD’, the context in which they are used clearly signifies that PAD is to be included. Although in general they require the same standards for allogeneic and autologous blood, they therefore do include additional ways of collecting and using autologous blood.

The Blood Safety Regulations

The Regulations apply to Blood Establishments and to hospital blood banks. From 8th November 2005 UK hospital blood banks are required to submit an application for authorisation to become a Blood Establishment if they collect or intend to collect autologous blood and blood components.

In these Regulations,

- “Autologous transfusion” means a transfusion in which the donor and the recipient are the same person and in which pre-deposited blood or blood components are used
- “Autologous donation” means blood and blood components collected from an individual and intended solely for subsequent autologous transfusion to that same individual.
- In summary, the Regulations and Directives indicate that where blood and blood components are collected and tested for the sole purpose and exclusive use in autologous transfusion and are clearly identified as such, the requirements to be complied with shall be in accordance with those for allogeneic blood donation described Directive 2004/33/EC, which include testing for
 - Hepatitis B (HBs-Ag)
 - Hepatitis C (Anti-HCV)
 - HIV 1/2 (Anti-HIV 1/2)
- Furthermore, autologous donations ‘shall be’ clearly identified and kept separate from allogeneic donations.

With reference to information to be provided to donors, the Regulations require

- the reasons for requiring an examination and health and medical history, and the testing of donations, and the significance of "informed consent"
- the possibility of deferral and the reasons why the donation procedure would not take place in the presence of a health risk to the individual whether as donor or recipient of the autologous blood or blood components
- Specific information on the nature of the procedures involved either in the allogeneic or autologous donation process and their respective associated risks.
- For autologous donations, the possibility that the autologous blood and blood components may not suffice for the intended transfusion requirements

- Information as to why unused autologous blood and blood components will be discarded and not transfused to other patients.

The specific requirements set out in the Regulations and Directives include:

Information to be provided to donors

Clear explanations must be specifically given as follows.

- the possibility of deferral and reasons why the donation procedure would not take place in the presence of a health risk to the individual whether as donor or as recipient of the autologous blood or blood component.
- the possibility that the autologous blood and blood components may not suffice for the intended transfusion requirements.
- information why unused autologous blood and blood components will be discarded and not transfused to other patients.
- the reasons for requiring an examination and health and medical history, and the testing of donations, and the significance of "informed consent".

Deferral criteria for autologous donors:

The following deferral criteria for autologous donation are in the Regulations

- Serious cardiac disease (depending on clinical setting of blood collection)
- Active bacterial infection

Testing:

Minimum blood group testing requirements are

- ABO Group
- Rh D Group
- Microbiology – see above

Member States may, however, establish more specific restrictions than these criteria and can thus vary from this legislation.

Processing:

Autologous donations should preferably be processed in the same way as allogeneic blood. Currently, when conducted in the UK, autologous blood is usually collected and processed in the same way as allogeneic whole blood. Leucodepletion may not be mandatory for PAD, but any processing of PAD whole blood in the UK will include leucodepletion, and blood components collected by apheresis - whether for autologous or allogeneic use - are leucodepleted to the same specification. It may be noted that although autologous blood is unlikely to be immunogenic, non-leucodepleted blood will release cytokines on storage and may cause non-haemolytic febrile transfusion reactions even in the autologous donor. Karger *et al* (2006), studying patients undergoing orthopaedic arthroplasty found that although leucodepletion of PAD blood by filtration is feasible, there are more incidences of slow filtration and indeed of filter failures: although the reasons are not clear, repeat collections from the same patient were consistent (either normal or delayed), indicating subject-specific factors. However, as the subjects are patients rather than donors their blood may be more likely to possess abnormal features.

Traceability:

Directive 2005/61/EC (due to be transposed to UK law in 2006) outlines the requirements for traceability and notification of defined serious adverse reactions and events; and requires that Blood Establishments and Hospital Transfusion Laboratories maintain for not less than 30 years the records pertaining to full traceability of blood, from collection from the donor to the ultimate fate of all components from that donation being transfused to the patient (including transfusion). (The data required is listed in Annex I of the Directive.)

The Directive also requires the reporting of serious adverse events and serious adverse reactions to the competent national authority (currently in UK the Medicines and Healthcare products Regulatory Agency - MHRA) in standard formats as outlined in Annex II of the Directive.

Traceability of PAD use is also covered by the Regulations and Directive.

Quality Systems:

Directive 2005/62/EC: (due to be transposed to UK law in 2006) sets out all the definitions, standards and specifications for quality systems for Blood Establishments (including those hospital departments authorised to conduct PAD) applicable to PADs. This Directive confirms that all PADs must be stored separately from allogeneic donations. PADs not transfused to the donor must be discarded and cannot enter the allogeneic blood pool.

Part 2. Literature analysis

Like all medical interventions, the use of PAD is time, country and circumstance dependent. The status of PAD in the medical armamentarium of any society may be reflected by the quality of the service for standard allogeneic blood transfusion in that society: this includes the cultural acceptability of allogeneic blood donation; the prevailing epidemiology; available resources (staffing, training, resource management etc); and general standards of clinical practice. International comparisons need to take these factors into account. Although the Guidelines described here are applicable to the conditions in the UK in 2006, much of the literature comes from overseas, and British reviews include reports from overseas.

Trials:

Although PAD has been advocated for decades, and such published advocacy was influential in the production of previous BCSH Guidelines (1993), more recent publications have been less enthusiastic. Few good quality randomised controlled trials have been published since 1993, and none from the UK; so the value and benefit of PAD remains controversial. Conflicting analyses are described by Hardy (2005).

In the study published by Billote *et al* 2002, of the 96 patients scheduled for primary total hip replacement surgery and who had a preoperative baseline Hb concentration (Hb) of 120 g/l or more who completed the study, 42 were autologous donors and 54 were non-donors. The Hb concentrations at enrollment, hospital discharge, and six weeks postoperatively were not significantly different between the two groups, although in the autologous group admission Hb (129 ± 13 g/L) and Hb in the recovery

room (104 ± 12 g/l) were significantly lower than in the non-donor group (138 ± 12 and 115 ± 13 g/L respectively - $p < 0.05$). No patient in either group required an allogeneic transfusion. Twenty-nine (69%) of the forty-two donors received an autologous transfusion. Thirty-four (41%) of eighty-two autologous units were wasted. At a charge of \$379 per autologous unit, there was an additional cost of \$758 for each patient in the donor group. Billote *et al* concluded that preoperative autologous donation provided no benefit for non-anemic patients undergoing primary total hip replacement surgery. Blajchman (2005) gave this study a relatively high score of 3 out of a possible 5 using the Jadad instrument.

A series of papers from Spain on the use of erythropoietin to boost haemopoiesis in adults and adolescents receiving spinal surgery (Garcia-Erce *et al* 2002; Garcia-Erce *et al* 2005) will be discussed below.

Reviews of clinical practices reported before 2000:

1. The American NHLI Transfusion Alert “Autologous blood guidelines for professionals” is useful and still available electronically but refers to no work published after 1994. They recommend that the possible need for allogeneic blood should be discussed with the patient, and state that most patients healthy enough to undergo elective surgery and with no medical contraindications to donation or storage of blood are healthy enough to undergo PAD. A haemoglobin concentration (Hb) greater than 110g/L is suggested. They recommend that PAD should only be considered when

- the likelihood of transfusion is more than 10%,
- elective surgery can be scheduled at least several weeks in advance
- the procedure is one for which blood is usually serologically matched.

Recommended indications for PAD include:

- Patients with bleeding tendency (but who are not currently anaemic or bleeding)
- Patients with allo-antibodies where allogeneic blood may be in short supply.

Contraindications include:

- Patients predisposed to bacteraemia, for example those with
 - an indwelling urinary catheter
 - a device penetrating the skin

Special considerations may apply when certain medical conditions co-exist:

- unstable angina,
- cyanotic congenital heart disease
- severe aortic stenosis
- severe occlusive cerebrovascular disease

They state that PAD can be safe for children although the volume collected should be reduced for body weight – as they assume a maximum tolerated blood loss to be 10% of the estimated blood volume. They report no complications for PAD in pregnancy, but PAD in advance of labour should be discouraged as the need for transfusion can rarely be predicted, placenta praevia being an exception.

2. A survey for the Council of Europe by Politis and Richardson 1997 reported activity in 27 countries. An estimated 4.2% of transfusions were autologous, mainly PAD, but there is much variance between countries and data is incomplete.

3. The International Society of Perioperative Transfusion (ISPO) has generated several systematic reviews examining the efficacy and safety of various technologies employed to minimize blood transfusions including PAD (Laupacis and Fergusson, 1998; Forgie *et al* 1998, Fergusson *et al* 1999). They reported the evidence, attitudes and practices relating to the use of alternatives to perioperative transfusion, and conclude that PAD, Acute Normovolaemic haemodilution (ANH) and cell salvage are associated with only small benefits in terms of reducing the need for allogeneic blood. Although PAD reduces exposure to allogeneic blood transfusion, it is associated with an increased in overall transfusion. Its benefits are directly related to transfusion rates in control groups for a number of surgical procedures: therefore inclusion of low risk procedures will not reveal the full potential of a given strategy.

More recent publications:

These include a review on peri-operative transfusion in elective surgery conducted by the Scottish Intercollegiate Guideline Network (SIGN study 54, October 2001, updated August 2004); and the Cochrane Collaboration Review by Henry *et al* 2003.

The SIGN guidelines conclude

- that PAD should be offered only when it is possible to guarantee admission and operative dates (to which they assign a 'D' Grade of evidence).
- PAD can be used to reduce allogeneic blood exposure although it does increase the total number of transfusion episodes (to which they assign an 'A' Grade of Evidence).
- PAD can be used safely in elderly population with diverse co-morbidities (to which they assign a 'C' Grade of Evidence).
- PAD should be targeted to men with Hb 110-145 g/l and women with Hb 130-145g/l (to which they assign a 'C' Grade of Evidence).
- PAD is not indicated for patients whose Hb is 145g/L or more and are undergoing primary hip or knee surgery (to which they assign an 'A' Grade of evidence).

The SIGN guidelines also consider the combination of PAD with erythropoietin and note that their recommendations are based on three small randomised controlled trials (RCTs). In fit patients undergoing major surgery they recommend that erythropoietin can be used in combination with autologous blood collection to reduce allogeneic transfusion, to which they assign a 'B' Grade Evidence. This is also supported by the NHLI 'Transfusion Alert' Guidelines. In fit patients undergoing major surgery, they report that erythropoietin can be used to obtain multiple red cell donations while maintaining an adequate haemoglobin concentration on the day of surgery.

Henry *et al* (2005) found that PAD reduced the overall risk of receiving an allogeneic blood transfusion by 63% (95%CI: 0.26, 0.54). The absolute reduction in risk of allogeneic transfusion was 43.8% (95%CI: -0.607, -0.268). In contrast the results show that the risk of receiving any blood transfusion (allogeneic and/or autologous) is increased by pre-operative autologous blood donation (RR=1.29; 95%CI: 1.12, 1.48).

Trials were unblinded and allocation concealment was not described in 87.5% of the trials. They concluded that although the trials of PAD showed a reduction in the need for allogeneic blood the methodological quality of the trials was poor and the overall transfusion rates (allogeneic and/or autologous) were high, and actually increased in those recruited into the PAD arms. This raises questions about the true benefit of PAD. In the absence of large, high quality trials using clinical endpoints, it is not possible to say whether the benefits of PAD outweigh the harms.

Rosencher *et al* (2001) reported a European study in elective orthopaedic surgery, where the 'wastage' (non-use) rate was very low as 90% of the PAD blood was used. Garcia-Erce and Munoz (2002), referring to this publication, point to general differences in health service provision between European and American societies, recommend that PAD provision be expanded and point out that according to the Code of Ethics for Blood Donation and Transfusion of the International Society of Blood Transfusion which is formally endorsed by the WHO, PAD should be explained and offered to all candidate patients. This raises concerns that need to be addressed further. Rosencher and Conseiller (2001) further indicate that although the risk of transfusion-transmitted infection by conventional viruses had become so small that cost/efficiency ratios had become 'exorbitant', the 'possible' transmission of Bovine Spongiform Encephalopathy (BSE) by transfused human blood could revive public health interest until 'the matter is settled'. After three reports associating the onset of vCJD prion infection in three residents of the UK who received blood donated by persons who subsequently developed confirmed vCJD (Health Protection Agency, 2006), this 'possible' risk has now become much more credible; but as most of the UK population born before 1996 has been exposed to BSE/vCJD environmentally, this is not a current concern for the majority of UK candidates. This debate will, however, have to be revisited as people born in the UK after 1996 come to require surgery – the 'herald' population are likely to include adolescents requiring spinal surgery during the next decade.

Brecher and Goodnough (2001) conclude that PAD is mostly a form of chronic haemodilution. They analyse the reasons for the fall in PAD use from its peak in the late 1980s and show that wastage rates are high. Their estimated Quality of Life Years gave costs of greater than \$50 000 for all types of surgery, reaching \$ 23 million for hysterectomy. As Popovsky *et al* (1995) reported that 1/16,783 PAD donors experienced very severe outcomes requiring hospitalisation, a rate 11.8 times higher than reported for allogeneic healthy donors, Brecher and Goodnough conclude that "judicious use of PAD in concert with other blood conservation methods in specific cases remains appropriate; however automatic referral of all patients for PAD is over simplistic and should be discouraged." They do not list the specific cases for which they consider PAD to be appropriate. They also comment that "should another risk of TTI be identified, or if blood collections fail to keep pace with demand for blood, the pendulum may swing back again."

Goodnough, Shander, and Spence (2003) echo the above and present the same data, concluding that although in most jurisdictions physicians are obliged to inform their patients about PAD it is not without cost and inconvenience. There is a 50% wastage rate and approximately 50% patients are anaemic on the day of surgery, making transfusion – autologous or even allogeneic – more likely. However they also state

“Nonetheless it is important to consider the patient’s peace of mind and informed choice”. In 2004, Goodnough commented that “the decision to employ blood-sparing technology may no longer be based on the safety of the blood supply, but on evidence that blood conservation is safe and of value for individual patients”.

In 2004 an unpublished report to the Clinical Audit and Effectiveness Unit of the English National Blood Service (NBS) Creswell undertook a re-audit of autologous collection services provided from the NBS Centre at Newcastle, covering the period June 1999 to May 2001. They concluded that “Children and young people undergoing scoliosis surgery have high blood requirements and may derive particular benefit from PAD. PAD is less use in other elective surgical procedures”. However the Newcastle hospitals were not using perioperative cell salvage at that time although it is now offered.

A similar unpublished NBS audit in Liverpool (Rushambuza and Godgeson, 2005) examined the appropriate use of PAD, and supported the recommendations suggested in ‘A National Blood Conservation Strategy’ for the National Blood Transfusion Committee and the National Blood service which recommended that

- PAD be offered to patients with rare blood groups and antibodies for whom it would be difficult to find allogeneic blood
- PAD be offered to patients whose mental health might be put at risk by using allogeneic blood
- blood transfusion, including PAD, at the time of allogeneic bone marrow harvesting for stem cell transplant be no longer recommended.

In the absence of large, high quality trials using clinical endpoints it is not possible to judge whether benefits of PAD outweigh harm. It should be noted that Popovsky *et al* (1995) reported an adverse reaction rate to autologous donation which was significantly higher than in allogeneic donors.

Iron supplementation and PAD:

The BSH Guidelines of 1993 recommend that “oral iron should be prescribed to all patients who pre-deposit before the first donation and continued until surgery.” More recent studies cast doubt on the efficacy of oral iron alone, particularly in the absence of prior anaemia.

Cid *et al* (2005) from Spain showed that neither oral iron nor folic acid supplements enhanced the accomplishment of their preoperative autologous blood collection program in patients with baseline Hb above 115 g/l.

Tseliou *et al* 2002 from Greece concluded that oral iron therapy in non-iron deficient patients undergoing a moderate program of three autologous units is not necessary.

Although Kasper *et al* 1998, from Germany concluded that oral iron supplementation increased the production of haemoglobin in autologous blood donors more than placebo, additional intravenous iron did not lead to a further increase in preoperative production.

If a candidate for elective surgery likely to need transfusion is found to be iron deficient, good clinical practice requires investigation for the cause of the deficiency

and treatment so that the candidate is iron replete prior to surgery (Andrews *et al*, 1997; SIGN, 2005).

Erythropoietin and PAD:

Although the BSH Guidelines of 1993 remark that the indications for erythropoietin in PAD are unclear and do not recommend it, several publications before and since have investigated this further, and particularly a combination of erythropoietin and iron (oral or intravenous). In the non-PAD setting, Goldberg *et al* (1996) describe two regimes for arthroplasty to boost haemopoiesis and reduce need for allogeneic blood; 300 u/kg daily subcutaneously for 14 days beginning 10 days preoperatively, or 600 u/kg subcutaneously three times weekly and on day of surgery. Both regimens are of proven benefit and seem equivalent in safety and efficacy. In conjunction with PAD, Brugnara *et al* (1993) found 200 u/kg/day subcutaneously boosted haemopoiesis in healthy iron replete men. Laupacis and Fergusson (1998) also comment that erythropoietin decreased exposure to perioperative allogeneic transfusion in orthopaedic and cardiac surgery but recommended further studies to establish the safety of erythropoietin alone, to determine the optimal dose of perioperative erythropoietin, and to compare its efficacy and cost-effectiveness with other methods of minimizing perioperative transfusion. However, Goodnough *et al* (1994) had shown that the desired increase in red cell volume could be predicted with intravenous erythropoietin therapy according to the formula RBC volume (ml per kg) = 6.34 + 0.0013X, where X equals total units erythropoietin administered (per kg body weight). The erythropoietin was given on six occasions within a three week period. Therefore in order to generate an extra 700ml red cells in a man weighing 70 kg, about 120,000 units of erythropoietin are needed *in toto*. According to prices quoted in the British National Formulary of September 1995, this would cost about £960 altogether. Brugnara *et al* (1993), in a study of healthy men, given erythropoietin 200U/kg/d for three weeks (294,000U – a cost of about £2300) was effective in enabling healthy men to donate blood (450 ml) twice a week for 3 weeks. See also Goodnough *et al* 1989; 1997 and 2003.

Weisbach and Eckstein (1996) concluded that the use of intravenous iron combined with erythropoietin seems to be justified to avoid ineffective erythropoiesis and to reduce the dose of recombinant erythropoietin. Furthermore, they suggest that oral iron supplementation may be applied to patients who tolerate it well, as there are ‘nearly no risks and a possible efficacy cannot be totally excluded’.

The SIGN review comments that the optimal dose of erythropoietin to support a PAD programme is still not known although it is undeniable that EPO (with iron) is effective in these circumstances. However, these courses are costly. As well as estimates quoted above, British National Formulary quotations indicate that for patients weighing 80 kg the doses recommended by Goldberg *et al* (1996) would cost approximately £2,600 for the 14-day course of 300 u/kg and approximately £1,600 for the course of 600 u/kg three times weekly. Erythropoietin treatment has always been accompanied by oral or intravenous iron therapy but an optimal iron support schedule has not been defined.

Garcia-Erce *et al* (2004) in a retrospective multicentre study of 680 adults and children undergoing spinal surgery advocated PAD with erythropoietin but reported wastage rates of 18% in scoliosis and 47% in spinal fusion.

PAD in children:

Mayer *et al* (1996) recruited 26 children median age 6 years (1 – 13) undergoing surgery mainly for digestive, urological or orthopedic defects, but could not venesect six of them – one through maternal apprehension and 5 through access problems. The remaining 17 participants were managed successfully.

Two recent publications, Franchini *et al* (2004) and Garcia-Erce *et al* (2005), support a combination of PAD and erythropoietin in children and adolescents undergoing spinal surgery. Garcia-Erce *et al* studied 75 children aged 10 to 18 years old. Those receiving PAD without recombinant erythropoietin – rHuEPO – (they tended to have higher Hb values) required allogeneic blood more often than those whose PAD was accompanied by rHuEPO treatment. The latter group were able to donate more blood and more were able to complete the PAD programme. Significant numbers of autologous units were unused by either sort of patient, more so among the rHuEPO recipients. The doses of subcutaneous rHuEPO varied between 600 u/kg twice weekly in those who were anaemic on entry to the programme, and 600 u/kg with each withdrawal and on the day of surgery for the others.

High risk and elderly patients:

In a study of 60 Swedish patients undergoing total hip replacement who were aged 60 to 82 years (mean 70), Elawad *et al* (1991) concluded that PAD from the elderly is safe and well tolerated, and encouraged the procedure in elective orthopaedic operations regardless of age. They also found that iron therapy (ferrous sulphate 100 mg three times daily) with or without folate supplementation (5 mg three times daily) reduced the preoperative decline of Hb compared with those who received no such therapy. Although the numbers were high for a single centre study, confirmation from multicentre studies with higher numbers is desirable.

Evidence that autologous blood donation is safe in high risk patients is reported by Cormack (1998), and by Hofmann *et al* (1992).

The cost effectiveness of PAD:

Many reports cast uncertainty as PAD can be associated with wastage rates of up to 55% of autologous blood units collected (Watson 2000). In an as yet unpublished Health Technology Assessment, Davies *et al*, 2006 describe six studies comparing economic evaluations of PAD with allogeneic blood use. Three (Birkmeyer *et al* 1994; Etchason *et al* 1995; and Marchetti and Barosi, 2000) indicated that PAD was not cost effective. Birkmeyer *et al* showed that PAD in patients having a coronary artery bypass graft produced limited health benefits at high societal costs, although some of the cost-inefficiency was 'strongly dependent' on estimates of post-transfusion hepatitis incidence but less so on HIV. They also observed that as blood gets safer, the relative costs of PAD increase, and that even a small estimate of fatality risk associated with PAD in a cardiac patient negates all life expectancy benefits of PAD. Etchason *et al* also reported that the increased safety of PAD use was limited and may not justify the cost; and Marchetti and Barosi reported that PAD alone was not more cost-effective than a do-nothing strategy. In contrast, the other three of the six studies claimed that PAD was cost effective. These were by Healy *et al* (1994), who reported net cost savings compared with use of allogeneic blood over a wide range of complication rates, patients' ages and transfusion requirements; Blumberg *et*

al (1996), who based their estimates on hospital charges in which the costs of autologous blood was approximately \$50 per unit while hospital costs increased by \$1000 to \$1500 per allogeneic unit used, and who found unsurprisingly that patients needing allogeneic blood on top of autologous had significantly higher hospital costs, to which increased length of stay added. They also felt that increases in post-operative infection (to which they assumed such patients were more susceptible as a result of receiving allogeneic blood) also contributed to their findings. The last of the three studies 'in favour' was that of Sonnenberg *et al* (1999) who, in a cost utility analysis, demonstrated that even if there were a modest increase in the risk of bacterial infection following allogeneic transfusion, PAD would result in improved outcomes at a cost-effectiveness that compares favourably to well-accepted health interventions. It has to be borne in mind that these analyses were undertaken in several countries in circumstances which may not prevail in the UK either at present or in the future.

The costs of erythropoietin therapy, even when perhaps ameliorated by concomitant iron therapy, add significantly to the costs of PAD. From the reports already quoted (Garcia-Erce *et al*, 2004; 2005) further doubt on PAD is cast by the significant wastage.

Part 3 :BCSH Guideline Recommendations:

Particular note needs to be taken of the specific developments in the UK, including:

- A developing consensus for conforming to the recommendations described in the UK Chief Medical Officers' recommendations described in 'Better Blood Transfusion 2'
- The increasing compliance with this as indicated by
 - audit
 - the current decline of issues of allogeneic red cells to hospitals in England (from 2,243,000 in 1999/2000 to an estimated 1,900,000 for 2005/2006.
 - The fact that all blood donors are non-remunerated volunteers
 - The current estimates of risks of infection transmitted by transfusion of allogeneic blood components from UK donors indicated in the Position Statement of the UK Joint Professional Advisory Committee, (see www.transfusionguidelines.org.uk) which are
 - 1 in 500 000 for HBV
 - 1 in 5 million for HIV
 - 1 in 30 million for HCV
- Continuing developments in surgical techniques resulting in reduced blood requirements
- Increased use of intra-operative autologous transfusion (for which further BCSH guidelines are being developed)
- Growing patient demand for alternatives to allogeneic blood transfusion

SPECIFIC RECOMMENDATIONS

Whole blood:

The use of PAD is **not recommended** unless the clinical circumstances are exceptional.

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Exceptional circumstances may include

- Rare blood groups where allogeneic difficult to obtain
- Children with scoliosis (Ib, A)
- Patients at serious psychiatric risk if blood transfusion is thought to be likely to cover their elective surgery (IV, C)
- Patients who refuse to consent to allogeneic transfusion but who would consent to PAD

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When PAD of whole blood is undertaken, the following criteria are required but do not of themselves justify it if they can be fulfilled.

- Patients considered for the procedure must be candidates for elective surgery, where blood transfusion is expected to be needed (Ib, A)
- The admission and operation days must be guaranteed (IIb, B).
- Sufficient time to enable optimal collection of the blood must be allowed prior to surgery, but should not exceed the licensed time for storing the collected blood component. For red cells this is in practice at least 5 weeks (IIa, B).
- Sufficient time should be given from the date and time of the ultimate PAD collection prior to surgery for the patient to make a full circulatory and volaemic recovery. The 15th Edition of the Standards of the American Association of Blood Banks (1993) recommend a minimal interval of 72 hours (IIb B)

Potential candidates

- should be judged by a competent clinician to be able to tolerate the repeated loss of the pre-determined volume of blood at each collection; this should normally be no more than 10% of their estimated blood volume (IV, C)
- should be provided with adequate information concerning the eligibility criteria for PAD and the reasons behind such criteria by the physicians providing the PAD service
- should be considered for supplementation with erythropoietin. (Ib, A):
- should present with the following Hb before embarking on PAD (III,B):
 - men, 110-145 g/l
 - women, 130-145 g/l
- For each individual case there should be a clear reason for preferring PAD to allogeneic blood as PAD is not indicated for most patients fulfilling the above criteria. Indeed the clinical indications for collecting and using PAD are limited: for the majority of patients undergoing elective surgery of a nature likely to require transfusion to treat surgical and post-operative blood loss, allogeneic blood is the preferred option.
- PAD is not recommended for children under 10 years old, mainly due to technical difficulties (large bore needle in veins of limited size) and it can be difficult to gain sufficient co-operation. (Ib A)
- Wherever appropriate, supplemental means of reducing use of allogeneic blood should be used, such as cell salvage.

Deleted: a

Candidates who meet the criteria for PAD but who are positive for relevant markers of transfusion-transmissible infection (TTI) present safety issues for staff collecting and processing the donations, and also potential for administrative and other errors. For these reasons, the Task Force **does not** recommend that PAD be offered to such patients unless they also fall into one of the exceptional categories.

Given the costs of erythropoietin its economic value to supplement PAD must be regarded as doubtful. The Task Force therefore **does not** recommend that erythropoietin be used unless the clinical circumstances are exceptional.

Although iron therapy prior to PAD has little effect on subsequent transfusion needs in individuals who are iron replete, there are advocates of iron therapy during PAD on *a priori* grounds though there is no good clinical evidence on which to base such recommendations. Therefore, the Task Force **does not** recommend prophylactic iron to iron replete individuals undergoing PAD (Ib, A), and further recommends that PAD be denied to persons who are iron deficient and receiving iron therapy until they have been effectively treated and their iron deficiency reversed.

PAD of red cell components collected by apheresis.

As the collection of allogeneic red cell component donations by apheresis becomes more widespread, autologous red cell component collection by apheresis may also be suggested. Allogeneic donors selected for red cell component collection (i.e by apheresis) may also be selected for greater volume and frequency of donation and therefore be heavier, have a higher blood Hb than for standard allogeneic donation (eg 140g/l), and have adequate iron status. However, there are no studies of such systems applying to PAD. The Task Force does not recommend that PAD be conducted by apheresis until and unless costs become comparable with those for standard donation collection and processing, and even then only under the exceptional circumstances pertaining to PAD by standard collection already considered.

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