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Blood Matters

Quarterly information for hospitals served by the National Blood Service

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Editorial

This edition of *Blood Matters* covers some really important ground. The first article on FFP provides an update on progress with regard to the provision of imported FFP for infants and children born after January 1996. Readers are aware that methylene blue (MB) treated UK FFP is already available in the UK for this group of vulnerable patients, providing a safer virally inactivated single unit FFP preparation. This next step of importing FFP (which will be MB treated on receipt) will provide additional protection against the possible risk of vCJD transmission to this group of patients who have not previously been exposed to the BSE-contaminated food chain. This is followed by a short article on replacement fluids for use in therapeutic plasma exchange procedures and flags up the recommendations in the new BCSH guidelines on the diagnosis and management of TTP. Then there is an article on a novel new component, autologous serum-derived 'artificial tears'. There is clearly a place for treatment with this new product and once operational and licensing issues have been addressed, there are plans to make this new product available to Eye Departments all around the UK, so watch this space.

There follows an article from the Royal Devon & Exeter Hospital which is an impressive illustration of how, by appropriate communication and enthusiastic co-operation, 'Better Use of Blood' can be achieved. Simple measures such as investigating every event where blood has been wasted, with follow-up and improvement of practice guidelines where necessary, can have a dramatic impact. The suggestion is that there should be a 'Handy Hints' column in future editions of *Blood Matters* so that relatively simple measures such as this can be shared amongst the readership, enabling a 'tool kit' of measures to be built up. This example will be used to set the ball rolling in this edition. As a helpful 'aide-memoire', a list of all the current transfusion medicine guidelines is published in this edition, together with summaries of the three most recent clinical policies prepared by the NBS Clinical Policies Group, including details of how to access them.

Finally, there is an article on the UK Blood Services policy on the provision of donated materials for non-therapeutic use. This has been in place for almost a year and has proved to be an invaluable source of guidance when requests are made for this type of material.

Following a suggestion from one of our readers, it is planned, from the next edition onwards, to include a CPD Quiz based on the contents of each edition. We are anxious that *Blood Matters* meets the needs of all its readers and in this edition there is a questionnaire with a reply paid envelope which I hope you will take the time to complete. We want to use your feedback to help improve the contents and style of this publication.

Dr Angela Robinson
NBS Medical Director
Contact email: *angela.robinson@nbs.nhs.uk*

Update On The Project To Provide Imported Methylene Blue Treated Fresh Frozen Plasma

Risk assessment of vCJD and FFP

At recent meetings of the Department of Health's (DH) Microbiological Safety of Blood and Tissues for Transplantation Committee, there has been discussion regarding the possible future sourcing of fresh frozen plasma (FFP) from outside the UK, as a precautionary step against transmission of variant Creutzfeldt-Jakob disease (vCJD). No proven cases of vCJD from transfusion have yet arisen, but experimental BSE has been transmitted by transfusion in sheep. The following points are relevant:-

- in some experimental models, plasma has been a source of low level infectivity, not removed by leucocyte-depletion
- there is a current working assumption that any infectivity remains constant throughout the incubation period
- the final number of vCJD cases in the UK over future decades is unknown. This could involve a number of blood donors.

A risk analysis of FFP, modelling a number of different scenarios, was performed by the DH Economic and Operational Research Group. In assessing possible non-UK sources of FFP, continuity of supply and maintenance of the highest possible level of overall safety were considered to be vitally important. In August 2002, the Department of Health announced that the UK would be seeking imported plasma for neonates and children born after 1st January 1996. The logic of selecting this patient group is that, due to various food bans, they should not have been exposed to the vCJD agent through food. Premature neonates in particular are both heavily transfused and have a long life ahead, so it is logical that they be protected first from any risk of acquiring vCJD by transfusion. The NBS has a project running to oversee implementation of this instruction. A specification for imported plasma has been produced, and we are currently considering tenders from potential suppliers. Any plasma which is procured will be from voluntary, non-remunerated donors in the United States, bled in Blood Centres licensed by the Food and Drug Administration, and selected and screened to nationally agreed standards. The specification includes a strong preference for plasma from untransfused males to minimise the risk of transfusion-related acute lung injury (TRALI). Since background rates of viral markers are higher in the United States than UK population, any imported plasma will be subjected to the methylene blue virus inactivation step which the NBS has already put in place for FFP for this patient group.

Methylene blue treatment

MB treatment is a photodynamic process which is applied to single units of plasma without the need to

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pool lots of donations together. This system is fully licensed, and is already in use in Spain and Scotland. The process includes an integral leucocyte-depletion step, and methylene blue is removed (>90% removal) prior to transfusion. The use of a single unit system ensures that the risks of certain viruses e.g. parvovirus B19, is no greater than currently. The system is effective against HIV, HBV and HCV, and is also active against West Nile Virus (WNV). It is unlikely to be effective against prion disorders. WNV is found across the USA, and is spread from birds to humans via mosquito bites. Although most cases are mild, the elderly and immunosuppressed may develop meningoencephalitis. In last summer's seasonal outbreak, there were a small number of possible transfusion-transmitted cases, but the risk of this is very low as viraemia is no more than a few days in donors without symptoms. US Blood Centres are taking additional steps to minimise the risk, and we anticipate that these steps, combined with MB treatment, will remove any risk from imported plasma.

In MBFFP, fibrinogen levels, measured by Clauss assay, show >30% reduction, but total clottable fibrinogen is normal and PT and APTT are in the normal range. Current quality monitoring data show that >90% of units have factor VIII levels above 0.7iu/ml, the UK standard for FFP. MBFFP has been shown to be efficacious in various clinical settings for which FFP is currently recommended. No randomised controlled trials of MBFFP have been performed, but over 3 million units have been used in Germany and Austria, with no reports of any reduction of clinical efficacy. However, a Spanish study has reported increased demand for FFP and cryoprecipitate following introduction of MBFFP. MBFFP and FFP usage is currently being monitored carefully by the NBS.

Manufacturers of MB systems have subjected MB to extensive toxicology testing. An independent report on these studies indicated that at the very low concentrations seen in MBFFP, no toxic effects would be predicted. As an additional safety step, a MB removal filter is used which removes >90% of MB without any detriment to coagulation factors. Glucose-6-phosphate dehydrogenase deficiency is not a contra-indication to the use of MBFFP, and its use does not interfere with the monitoring of blood oxygen levels using colour-sensitive pulse oximetry.

The project team is currently performing an assessment of the feasibility of producing cryoprecipitate and cryosupernate from MB-treated plasma

Future plans for safer FFP

To date, the NBS has not received any instructions from the Department of Health regarding provision of imported/virus inactivated FFP for other patient groups. Hospital clinicians who would like to use MBFFP for older patients should discuss this with their NBS Link Consultant. Solvent-detergent FFP (SDFFP) is available to hospitals directly from the suppliers.

A new project is also underway to assess the optimal means of reducing the risk of transfusion-related acute lung injury (TRALI) following transfusion. TRALI is a syndrome of acute dyspnoea and hypoxia with pulmonary infiltrates, coming on during or within 2-6 hours of a transfusion. It is clinically and radiologically indistinguishable from adult respiratory distress syndrome. In the classic description, donor plasma containing leucocyte antibodies (HLA or granulocyte-specific) is implicated, and most series identify 1 or more positive donors in >80% of cases. The frequency for recipients of plasma-containing components has been estimated at 1 in 5-10,000. This is consistent with reports to the Serious Hazards of Transfusion (SHOT) scheme, which receives over 20 reports of TRALI each year, some fatal, although in some cases other causes of acute lung injury cannot be excluded. FFP and platelets are implicated in >50% of cases.

Although TRALI can occur after any blood component, risks from plasma-rich components (FFP and platelets) are much higher than those from red cells. Options under consideration include 'male-only' FFP, the use of additive solution to replace 70% of the plasma in platelet concentrates, and HLA antibody screening of donors of certain products. It has also been suggested that pooled SDFFP would have a lower or even no risk of causing TRALI, because of the dilution of high titre antibodies in the donor pool. Certainly no cases of TRALI with SDFFP have been reported in the literature or to SHOT, but no comparative trials have been done. We will update you on the progress of this work in a future edition.

Appropriate usage of FFP

Figures 1 and 2 show the age distribution and hospital specialty of FFP recipients in a pilot survey of 5 hospitals. These show that while FFP is widely used across hospital specialties, there is considerable usage in cardiac and general surgery. A number of audits of the use of FFP have been carried out in recent years. They are summarised in Table 1.

The audits show that between 62 and 92% of transfusions of FFP were considered to comply with the current BCSH guidelines on the use of FFP. New guidelines on the clinical use of FFP are expected later this year (2003). 33-58% of transfusions were below the recommended dose of FFP. Several audits commented on poor documentation of the indication for the transfusion.

The most obvious approach to minimising the number of patients at risk of the complications of FFP is to ensure that it is only used when clinically appropriate. We encourage each Hospital Transfusion Committee to review the usage of FFP in their hospital(s), and to take action to avoid its unnecessary use.

Six local audits of FFP use are summarised in Table 1. These data has been kindly provided by Valerie Burrowes-King and Dorothy Stainsby (NBS Clinical Audit).

The audits all used BCSH guidelines as the standard and were conducted between 1993 and 2001, with study periods ranging from 2 weeks to 12 months. One was a regional audit carried out in 1993. The majority did not specify whether patients were adults, children or neonates. Where this information was provided it is illustrated in the Table. The total number of patients studied was 493.

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Compliance with BCSH guidelines

- The highest level reported was 92% compliance with BCSH guidelines. This was achieved in an audit conducted on 39 patients over a 6-month period, in 1997.
- The lowest level of compliance reported was 62%. This later audit in 1999 studied 45 patients over a 3-month period. However on re-audit the following year compliance had increased to 80% in the 60 patients studied.

Effective audit interventions

- An improvement in compliance with BCSH guidelines from 62% to 80% was achieved at one Trust by implementing a programme of feedback and discussion. Compliance with dosage recommendations was improved by the use of a dose/weight chart in the laboratory.
- 92% compliance with BCSH guidelines was achieved by another Trust by screening requests at laboratory level.

Problems identified by audits

- Between 16% and 58% of FFP transfusions were below the recommended dose.
- Unsatisfactory documentation of FFP transfusions was highlighted in 4 audits.

Dr L Williamson
Lead Clinician for Components
Contact email: *lorna.williamson@nbs.nhs.uk*

Dr M Murphy
Lead Clinician for Hospital Liaison
Contact email: *mike.murphy@nbs.nhs.uk*

Figure 1. *Age distribution of FFP recipients (n=361)*

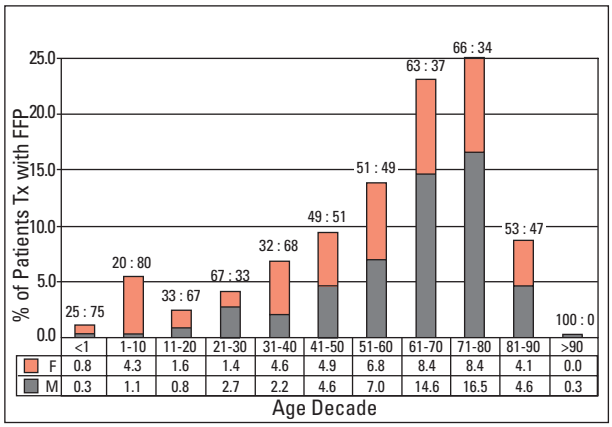

Figure 2. *FFP use in 5 hospitals (2005 units) by hospital specialty*

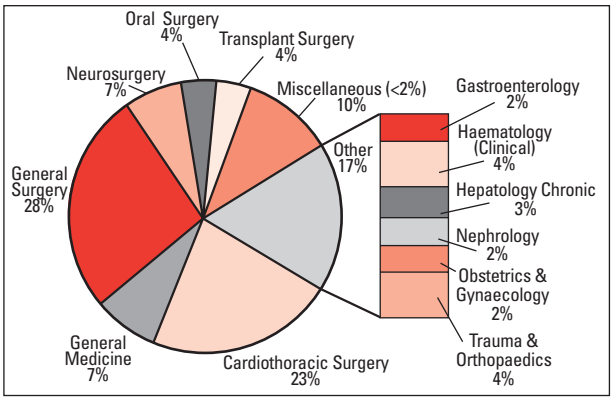

Table 1. *Summary of recent audits of the use of FFP*

Hospital Audit Code	Based on BCSH Guidelines	Audit date	Time period of audit	Transfusions deemed appropriate	No. of patients. Transfused	No. of units Transfused.	Comments
ST48	Yes	Jan 2000 – Jun 2000	6 months	75%	107	146	58% of transfusions below the guideline dose 30 transfusions had no documented indication for transfusion.
MA17	Yes	April 97 – Sept 97	6 months	92%	39	134	All requests screened at laboratory level resulting in high compliance with guidelines. General Medicine is the highest user. Wastage is high – 14.9%. Transfusion records are unsatisfactory.
LI04	Yes	Nov 2000 – Feb 2001	3 months	80%	33 1 neonate	170 1 paedi-pack	Increasing use over the past 5 years – most requests from the Medical Directorate. Report pending.
CA06 (1st audit)	Yes	Oct 99 – Dec 99	3 months	62%	45	117	The appropriate dose was transfused in 33% of the 73 FFP transfusions which had a recognised indication for transfusion. 49% of patient's notes stated the indication for transfusion.
CA06 (re-audit)	Yes	Sept 00 – Nov 00	3 months	80%	60	102	61% of transfusions were of appropriate dose. 46% reasons for transfusion documented.
OX08	Yes	Feb 2000 - March 2000	5 month	79%	31 Adults 7 Children	194	84% correct dose. 60% correct indicator and dose.
SH11	Yes	1993 – 1994	12 months	Not known	170	Not known	Relevant coagulation test performed before request in 90% cases. Poor documentation in patient case-notes highlighted.

Component Therapy in Therapeutic Apheresis Procedures

Therapeutic apheresis involves the physical removal of abnormal blood constituents for the purpose of alleviating or controlling disease symptoms. The following types of therapeutic apheresis procedures are undertaken in some of the apheresis units within the NBS - red cell exchange, plasma exchange, leucapheresis, photopheresis and LDL apheresis[1].

In the six months from April 2002 to September 2002 inclusive, a total of 27 red cell exchanges and 757 plasma exchanges were undertaken by the apheresis units within the National Blood Service.

Principles of Replacement Therapy

All therapeutic apheresis procedures are used in conjunction with disease modifying treatment for the underlying condition. The principles of replacement therapy ensure that the patient is kept in fluid balance, neither overloading nor dehydrating the patient. In working out the volume of fluid to be replaced, a minimum of one plasma volume per procedure is used for predominantly intravascular material or one total blood volume for red cell exchange. One plasma volume would usually remove about 66% of the circulating intravascular contents, while two plasma volumes would remove about 85%. In practice between one and one and a half plasma volumes are exchanged with each treatment procedure.

Replacement Fluids

The replacement fluid for plasma exchange is usually 4.5% human albumin solution. Substitution of 25 - 50% of the replacement fluid volume with normal saline has been reported by some groups.

Fresh frozen plasma (FFP) is only used where there is evidence that it works better than albumin. To date, the only condition where FFP is recommended as replacement fluid is in thrombotic thrombocytopenic purpura (TTP) which deserves special mention.

For all other procedures, albumin is used as replacement fluid except for patients with a pre-existing bleeding diathesis who may not tolerate the temporary deficiency of clotting factors post-exchange, or for patients who have had a recent biopsy. Albumin is pasteurised, independent of blood group, does not require any thawing or special preparation, gives fewer complications of infusion and there is no extra infused citrate (as in FFP).

Other plasma substitutes such as Gelofusine have been used in anecdotal reports of single plasma exchanges in Jehovah's Witnesses for example. However, large volumes can increase the risk of bleeding through depletion of coagulation factors.

TTP

The recently published BCSH Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias[2] confirm that the optimal replacement fluid in this condition remains contentious. Cryosupernatant (plasma from which cryoprecipitate has been removed) is at least as efficacious as FFP. A large randomised controlled trial comparing plasma exchange with FFP versus cryosupernatant is currently being performed in Canada. Solvent detergent treated (S/D) plasma not only reduces viral risk but may be beneficial in reducing allergic reactions. S/D plasma has a similar favourable multimer profile to cryosupernatant and has been used as replacement fluid in TTP. However, there is no published comparative data with FFP or cryosupernatant.

Further clinical experience is required to ascertain the role of S/D plasma in the primary treatment of TTP. There is evidence, however, that refractory cases of TTP do respond to the substitution of cryosupernatant FFP with S/D plasma or an alternative replacement fluid, such as methylene blue treated plasma. The experience of this is small at the present time.

Conclusion

The above are the broad principles to which the Therapeutic Services work within the National Blood Service. Newer immunoadsorption techniques are currently being developed which do not require any fluid replacement. During these procedures, the pathogenic substance causing the disease is selectively removed from either whole blood or plasma while all the remaining constituents of blood are returned to the patient. This removes the need for any replacement with colloid solutions e.g. LDL apheresis for hypercholesterolaemia using either the DALI or Kaneka machine.

References

1. National Blood Service Clinical Guidelines for Therapeutic Apheresis (internal NBS document only)
2. BCSH Guidelines on the Diagnosis and Management of the Thrombotic Microangiopathic Haemolytic Anaemias. BCSH Website July 2002 (*http://www.bcshguidelines.com/*).

Further Reading

Blood Matters, Issue 10, 2002, pages 9-11.

Clinical Applications of Therapeutic Apheresis. Journal of Clinical Apheresis, Vol 15, Issue 1-2 (special issue), 2000.

Dr Moji Gesinde
Lead Consultant Apheresis
Contact email: *moji.gesinde@nbs.nhs.uk*

Autologous Serum-Derived "Artificial Tears"

Over the last 3 years, research into a novel use of autologous blood has been undertaken at Leeds Blood Centre, in conjunction with the Department of Ophthalmology at Leeds General Infirmary. This involves using autologous serum to manufacture "artificial tears" for patients with severe dry eye conditions.

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Tears act as a simple lubricant, which prevent the ocular surface from drying up and protect the eye from irritation caused by blinking. They also contain growth factors such as epidermal growth factor, transforming growth factor beta (TGF–β). fibronectin and vitamin A which perform antibacterial and healing functions. Some patients, for example those with keratoconjunctivitis, Sjogrens Syndrome and bone marrow transplant-induced chronic graft-versus-host disease, lose the ability to produce adequate tears, resulting in severe morbidity. The only treatment options open to these patients is the use of artificial tears (consisting of saline, a lubricant and preservative) with the adjunct of punctal occlusion in some patients. Many patients fail to get adequate relief from these treatments and some in addition develop hypersensitivity to preservatives used in artificial tears.

In the early 1980s it was suggested that fibronectin, a constituent of serum, may be involved in wound healing as it is found beneath healing corneal cells and is thought to be responsible for cellular adhesion. Purified fibronectin was found to be beneficial in the healing of rabbit corneal wounds [(1)] but the purification process was complex and expensive. In 1984 the use of serum-derived drops, which contain fibronectin in addition to other growth factors, was first reported in patients with keratoconjunctivitis sicca [(2)]. Since then several reports have described the use of autologous serum applied as eye drops, mostly for improving wound healing after surgery or treatment of persistent corneal ulcers. A recent clinical study showed benefit in patients with keratoconjunctivitis sicca and persistent epithelial defects [(3)].

We have developed a method for the production of autologous serum-derived tears (in accordance with the principles of Good Manufacturing Practice) and performed a randomised crossover study comparing the use of this product with conventional therapy in 16 patients. This study has shown that most patients' symptoms were significantly improved when using the autologous serum drops as compared with conventional therapy, and that some patients derived dramatic benefit.

To be suitable for this treatment, patients must fulfil criteria to donate autologous blood in accordance with the BCSH Guidelines for Predeposit Autologous Donation [(4)]. Blood is collected into a sterile dry pack and allowed to clot. Serum is separated and diluted 1:1 with saline – the diluted saline is then aliquotted into sterile glass dropper bottles and frozen. Patients are instructed to remove one bottle from the freezer for use that day and to discard the bottle at the end of the day (to minimise the risk of bacterial contamination).

There is considerable interest in this treatment amongst ophthalmologists around the UK. A questionnaire was recently distributed to a sample of Consultant Ophthalmologists, results of which suggest that there is likely to be a significant demand for this product from most areas of the country. When operational and licensing issues are addressed it is proposed to offer an 'autologous tears' production service to Eye Departments in other hospitals supplied by the NBS. Ophthalmologists and Blood Banks will be kept informed of progress with this Project over the next few months.

References

1. Fujikawa LS, Foster CS, Harrist TJ et al: Fibronectin in healing rabbit corneal wounds. Lab Invest 1981; 45: 120 – 129.
2. Fox RI, Chan R, Michelson JB et al: Beneficial effects of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis and rheumatism 1984; 27(4): 459 – 461.
3. Poon AC, Geerling G, Dart JKG et al: Autologous serum eyedrops for dry eyes and epithelial defects: clinical and in vitro toxicity studies. Br J Ophthalmol 2001; 85: 1188 – 1197.
4. British Committee for Standards in Haematology Blood Transfusion Task Force: Voak D, Finney RD, Forman K et al: Guidelines for autologous transfusion. I. Pre-operative autologous donation. Transfusion Medicine 1993; 3: 307 – 316.

Dr Sheila MacLennan
Consultant in Transfusion Medicine
Contact email: *sheila.maclennan@nbs.nhs.uk*

Communication, Co-operation and the Rational Use of Blood

Introduction

The Royal Devon and Exeter is a busy district general hospital with recently acquired teaching hospital status. Despite a near doubling of the number of surgeons and an increase in complex procedures over the last ten years, blood consumption has remained static, whereas the cross-matched to transfused (C:T) ratio has improved (Figure 1). Overall blood wastage has reduced to 0.5 % of units issued to the trust (Figure 2). We have been asked to outline some of the factors that contributed to a more rational use of blood transfusion.

Figure 1. *Static Red Cell Consumption and Falling C:T ratio 1988-2002*

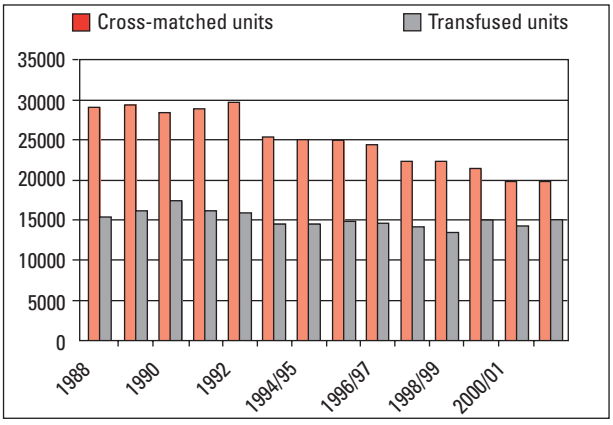

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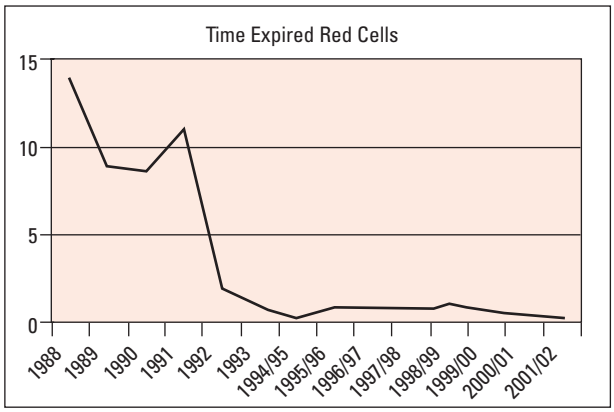
Figure 2. *Percentage reduction in wasted red cell units 1988-2002*



Blood Stock Management

Medical patients, and in particular haemato-oncology cases, are heavy consumers of blood and ensure a rapid turnover of available stock therefore minimising units approaching expiry. Several methods have been introduced to increase efficiency and to reduce waste. These include:

- Selecting oldest red cells if their use is certain
- "ASBOS" (see below)
- Immediate spin cross-match
- Next day return of unused red cells
- Lower stocks
- Reducing the number of red cells crossmatched but not used
- Credits for time expired AB units

Every event where blood has been wasted is investigated and all the staff involved are interviewed. A clinical incident report is completed and the line manager or clinical director informed. The incident is discussed at the HTC and, if appropriate, procedures and protocols are revised.

The Hospital Transfusion Committee

This is a lively forum with enthusiastic representation by clinicians, managers and blood bank staff. There is regular, accurate feedback to clinicians, including individual firm's blood wastage and crossmatch to transfused ratios. These data are presented at departmental audit meetings which leads to debate and peer pressure.

The hospital wide MSBOS is reviewed regularly in the light of audit and feedback. We now call this the ASBOS (Agreed Surgical Blood Ordering Schedule) to reflect the discussion which has taken place between individual surgeons, anaesthetists and the blood bank for each type of procedure. Almost all elective surgery is now done with a "group and save" alone.

The Hospital Transfusion Team

As recommended by BBT2 we have set up a pro-active team consisting of a consultant haematologist, blood bank manager and the clinical blood conservation co-ordinator (see page 8). Other staff, such as intensivists and the clinical audit team, are co-opted when necessary. Meetings are held monthly and the HTT reports on matters of training, audit, transfusion incidents, SHOT and continuing quality development.

Crossmatch on Demand

Several years ago audit revealed that red cells cross-matched for patients with a fractured femoral neck, or patients undergoing primary THR or TKR, were only used on those patients with low pre-operative Hbs. We introduced a laboratory led initiative whereby those patients with an Hb concentration > 12g/dl did not have blood cross-matched. The decision was taken out of the hands of the junior doctors. A recent audit has shown that although red cells were available for these patients with low Hbs while they were in theatre it was rarely used at that time and were therefore returned to stock the next day. Blood was then requested post operatively requiring reissue or rematching of red cells. The ASBOS for these procedures has now been revised to "group and save" for all patients. If blood is required during or after the operation it is cross-matched using the immediate spin technique. This approach has now been extended to many other procedures. Patients with irregular red cell antibodies always have red cells crossmatched in advance. Communication and portering support is of course vital to success. Our experience of this over the last three years has been:

- No problems obtaining blood during surgery
- Less blood wasted
- No morbidity or mortality associated with the approach
- Most transfusions required postoperatively
- Cell salvage essential for back-up

Crossmatch on demand is now used in colorectal and urological surgery.

Cell Salvage and Autologous Blood

We have been blood conservation enthusiasts for more than ten years. Cell salvage is routine for vascular surgery, orthopaedics and urology, which is now the major indication. Cell salvage has been in use for malignancy for eight years and is especially useful in cystectomy and radical prostatectomy. We do not ultrafilter or irradiate blood and have not encountered an increase in pulmonary metastasis. Cell salvage is particularly useful in the irradiated pelvis, which tends to ooze during surgery.

The second on call ODP is responsible for emergencies and the hospital has a consultant led trauma team whose leaders are aware of cell salvage.

Salvage is the essential safety net for the "crossmatch on demand" service as it is particularly useful in the unlikely event of unforeseen (what is euphemistically described as "technical") bleeding. The collection reservoir is set up initially, with the process software only being opened when sufficient blood has been collected. This saves on costs and allows one machine to be shared between theatres.

Other autologous techniques have been explored. Erythropoetin was not introduced as few patients were

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suitable. Pre-deposit was abandoned due to logistical problems and unease that we were operating on patients with iatrogenic anaemia. Haemodilution is the subject of an ongoing randomised trial (co-ordinated in Exeter) and postoperative wound drain reinfusion has been introduced.

Blood Management

Blood conservation is promoted amongst junior surgical and anaesthetic staff with jointly agreed triggers to transfusion. This has decreased inappropriate transfusion especially in the postoperative period. Techniques such as warming of patients, fluids and anaesthetic gases are routine.

Our business managers have been far sighted and have agreed to budgetary transfer between directorates to introduce many of our initiatives.

The Clinical Blood Conservation Coordinator

Dr Biddy Ridler has been appointed by the trust to this substantive post at staff grade level with the aim of introducing the requirements of the BBT2 NHSE directive. Her job description is broadly based but the most important elements have proved to be:

- Bridge building between specialties
- Changing attitudes in a non-confrontational way
- Troubleshooting transfusion incidents
- Understanding others' roles
- Education (rotating between departments)
- Audit (SHOT, intra-operative cell salvage [ICS] quality control and autologous database)
- A referral point for all matters relating to transfusion policy

Dr Ridler also runs the Vascular Surgical Society National Vascular Database which includes information regarding blood transfusion and clinical outcomes, which will provide useful results in the future.

Conclusion

There are many cost neutral, low tech. interventions which can reduce blood wastage, increase efficiency and reduce costs. All that is required is an interested multidisciplinary group. Improved clinical outcomes are an obvious quality issue which should drive the changes forward, but constraints on the blood supply may force the argument.

Our only concern is that if Trusts are asked to decrease their blood consumption by, say 15%, then those who have introduced "blood management" successfully will find this very difficult to achieve.

BMF Ridler MB BS,
Clinical Blood Conservation Coordinator
S Elcoate FIBMS, Blood Bank Manager
JF Thompson MS FRCS, Consultant Surgeon
Royal Devon and Exeter Hospitals
Contact email: *j.f.thompson@exeter.ac.uk*

NBS Clinical Guidelines

Communications from the NBS Clinical Policies Group (CPG, chaired by Dr Neil Smith) are available on the NBS website (www.blood.co.uk/hospitals/index.htm) and have been sent to hospitals, but it was thought that a summary here might be of further help.

At the bottom of the Home Page are 8 icons ('idealised' blood packs). One is labelled "Library". Clicking on this brings up the "Table of Contents". On the left hand side is "Guidelines". Clicking on this brings up the Clinical Policies Group page, near the top of which is the "Index of Clinical Guidelines". Currently there are five guidelines: ABO and RhD compatibility in platelet transfusion; the use of O RhD negative red cells; the provision of components negative for high titre anti-A/B antibodies; the management of platelet transfusion refractoriness; Transfusion Associated Graft Versus Host Disease. Summaries of the first two are given in *Blood Matters* No.5 (December 2000). There follows a summary of the other three. All were approved by the CPG in 2002 and will be reviewed no later than 2004. A complete list of all current Transfusion Medicine Guidelines will be found at the end of this article.

High titre anti-A/B testing of donors.

This applies to *donations*, and is to minimise the risk to patients of significant haemolysis from passively transfused high titre anti-A or anti-B antibodies. Although this can occur when components of group A, for example, are transfused to patients of group B, the vast majority occurs after transfusing components containing plasma from group O donors to non-group O patients. The paper cites 12 reports of 13 cases of proven haemolysis; 4 patients were under 4 years old - one of these was a 6-day-old baby of blood group B who was affected even though the O red cells given were resuspended in AB plasma. (None of the case reports implicate cryoprecipitate which can nevertheless cause haemolysis even when pooled - as once witnessed in a young mild haemophilic (Group A) who, in 1979, received repeated doses.)

The risk of such haemolysis from NBS components will be minimised by the recent adoption of a national policy for detecting "high titre" anti-A or anti-B donations in our grouping systems (Olympus). Components with this reactivity should not be transfused to any patient who is not of the same group as the component. Units which the NBS labels "NEG:HT" have no reactivity in this system. Components labelled "for neonatal use" do not have 'high titre' antibodies even if not specifically stated as the specification for neonatal components requires them to be HT negative in addition to other requirements. Note: some unreactive units do not get labelled (enough get labelled); also note that reactive components are NOT labelled to indicate 'High Titre Reactivity', therefore all undesignated units should only be used for the same group.

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Finally: haemolysis can never be eliminated completely in group A, B, or AB patients receiving plasma-containing components from donors whose ABO group is different from theirs. This may occur, for example, when large volumes (large relative to patient size) of HLA-matched platelets are transfused to one individual. Wherever possible, therefore, ABO-same components should be transfused. The only exception is AB FFP which is free from ABO haemolysins and is mainly used for neonates. Any suspected case of haemolysis due to passive transfer of ABO antibodies should be reported to SHOT, and also to your local NBS Blood Centre if possible, as it is important to monitor the effectiveness of this testing policy in preventing this complication. This guideline complements the earlier guidelines on the ABO groups of transfused platelet concentrate which should be read carefully (see also *Blood Matters* Issue 5).

Transfusion Associated Graft Versus Host Disease (TAGVHD)

This is based on a review of literature and of currently accepted practices; its purpose is to recommend the appropriate investigation and clinical advice for cases of suspected or proven TAGVHD. This is a rare but usually fatal condition. At-risk patients include fetuses, children with SCID, those with DiGeorge syndrome or related disorders transfused for cardiac surgery, stem-cell transplant recipients, and people with Hodgkin's lymphoma. Solid organ transplantees, and patients with HIV and solid tumours are not at risk; but to cover uncertainties regarding patients with non-Hodgkin's Lymphoma, check the latest guidelines from the British Committee of Standards on Haematology. The number of lymphocytes in the transfusate is also a pre-disposing factor, but leucodepletion (LD) does not prevent TAGVHD absolutely. This is best achieved by gamma-irradiation (25 Gy) to any part of the blood component container. FDA trials of blood components treated with Psoralen (S59) and UVA light to prevent TAGVHD are being conducted. Adults and older children 'at-risk' should carry an appropriate Department of Health card.

Clinical features (skin rash, fever, diarrhoea liver, dysfunction, marrow failure etc) appear one to two weeks after transfusion. As TAGVHD results from the engraftment and proliferation in the recipient of donor lymphocytes, diagnosis relies principally on the demonstration of mixed chimerism. This is more likely to occur when there is substantial HLA matching between donor and recipient. Management requires prompt treatment; several drugs including cyclosporin A, methotrexate and steroids have been used. Other agents are available but their roles are uncertain. Mortality is greater than 90%.

For investigations, samples are required from donor and recipient, the latter including if possible, pre-transfusion samples (any amount); even hair follicle or nail clippings in saline taken after transfusion are sources of pre-transfusion DNA. All samples can be analysed within NBS facilities.

A more common management problem is how to manage asymptomatic at-risk patients who have recently received non-irradiated components (often inadvertently, but recognised in retrospect). Apart from reporting to SHOT and establishing which components are involved, it is important to establish the patient's HLA type and to store mononuclear cells. There should also be careful clinical observation of the recipient and rapid institution of treatment if any clinical features appear. This is by no means inevitable.

Management of platelet transfusion refractoriness

The purpose is to define and recommend policies and procedures for optimal transfusion support to patients refractory to unselected platelet components. Refractoriness may be immune or non-immune in origin so it is important to identify transfusion failures due to HLA alloantibodies clearly, and exclude non-immune mechanisms. It is also important to identify patients with other antibodies including HPA and (rarely) auto antibodies. The TRAP study showed that alloimmunisation occurs in 45% of recipients but immune refractoriness only in 13%. LD reduces alloimmunisation to 10-25% (so immune refractoriness should be less frequent than when non-LD products are used); most patients are women exposed to HLA alloantigens from previous pregnancies.

There is an algorithm, and early prospective class HLA 1 typing is recommended. Poor responses to platelet transfusion may suggest antibodies requiring the use of matched platelets. Samples required for investigation within NBS facilities are 5 mls of clotted plus 5-10mls of EDTA or citrated blood. These can be sent to the local blood centre.

The biology and anthropology of HLA mean that matching is at best relative. The guidelines define 'type of match' (4, 3, 2, 1, 0 serologically compatible antigens) but clinicians would be wise to be unsurprised by suboptimal performances even following transfusion of Type A matched platelets (4 compatible antigens).There are other HLA loci, and 'minor' antigens genetically unrelated to HLA which may confound expectations. Nevertheless, serological 'crossmatching' of HLA-matched components is not recommended as a routine.

We all know that many requests for help in managing refractoriness arrive on-call, commonly late Friday afternoon. This can be difficult if there is no prior warning, although we recognise that patients are unpredictable. However, clinical anticipation is always appreciated. All requests [for new referrals] should be discussed with and approved by the clinical consultant on-call at each NBS Centre. The NBS user guide can supply details regarding provision of matched platelets. It is NBS policy to irradiate all HLA platelets before issue.

Dr Frank Boulton
NBS Southampton
On behalf of the Clinical Policies Group
Contact email: *frank.boulton@nbs.nhs.uk*

Transfusion Medicine Guidelines in UK

Title	Date Issued/due	Source
BCSH Guidelines		
Administration of Blood and Blood Components and the management of transfused patients	Sept 1999	Transfusion Medicine, 9:227-238
Autologous Blood Transfusion I	Dec 1993	Transfusion Medicine 3:307-316
Autologous Blood Transfusion II	June 1997	Brit J Anaesthesia 78:769-771
Blood Bank Computing	2000	Transfusion Medicine 10:307-314
Blood Grouping and Red cell antibody testing during pregnancy	March 1996	Transfusion Medicine 6:71-74
Clinical use of Cell Separators	1998	Clin Lab Haematol 20:265-278
Clinical Use of Leucodepleted Blood	March 1998	Transfusion Medicine 8:59-71
Collection, Processing and Storage of Stem Cells	June 1994	Transfusion Medicine 4:165-172
Evaluation, validation and implementation of new blood grouping techniques	June 1995	Transfusion Medicine 5:145-150
Fresh frozen Plasma	March 1992	Transfusion Medicine 2:57-63
Fresh Frozen Plasma 2nd Ed	May 03	www.bcshguidelines.com/
Hospital blood bank documentation and procedures	1990	Clin Lab Haematol 12:209-220
Investigation of Thrombycytopenia in pregnancy and NAIT	1996	Brit J Haem 95:21-26
Irradiation of Blood Components	Sept 1996	Transfusion Medicine 6:261-271
Management of adverse reactions to transfusion	March 03	www.bcshguidelines.com/
Maximum Surgical Blood Ordering Schedule (MS-BOS)	1990	Clin Lab Haematol 12:321-327
Platelet Transfusion	Dec 1992	Transfusion Medicine, 2:311-318
Platelet Transfusion 2nd Ed	May 03	www.bcshguidelines.com/
Pre-Transfusion Compatibility Procedures	Sept 1996	Transfusion Medicine 6:273-283
Product liability for the hospital blood bank	1990	Clin Lab Haematol 12:329-344
Red Cell Transfusion	2001	Brit J Haem 2001:113, 24-31
Transfusion for massive blood loss.	1988	Clin Lab Haematol 10, 265-273
Transfusion to Neonates and Infants	March 1994	Transfusion Medicine 4:63-69
Transfusion to Neonates and Infants 2nd ed	March 03	www.bcshguidelines.com/
Use of anti-D immunoglobulin	March 1999	Transfusion Medicine 9:93-97
NBS Clinical Policies Group		
Clinical significance of red cell antibodies	Feb 2003	NBS CPG Website www.blood.co.uk/hospitals/index.htm
Guidelines for the management of platelet transfusion refractoriness	April 2002	NBS CPG Website
High titre anti-a/b testing of donors within the National Blood Service	April 2002	NBS CPG Website
Management of multiply transfused patients	Feb 2003	NBS CPG Website
The ABO and RhD compartibility in relation to platelet transfusions	2000	NBS CPG Website
The use of Group O negative blood	2000	NBS CPG Website
Transfusion mangement of IgA deficient patients	Feb 2003	NBS CPG Website
Transfusion-associated graft-versus-host disease	April 2002	NBS CPG Website
Other sources		
Blood transfusion and the anaesthetist – red cell transfusion	Sept 2001	www.aagbi.org/pdf/blood_tran.pdf
Guidelines for non-variceal upper gastrointestinal haemorrhage British Society of Gastroenterology Endoscopy Committee		www.bsg.org.uk/clinical_prac /guidelines/nonvariceal.htm
Investigation of patients with auto-immune haemolytic anaemia and provision of blood for transfusion	July 1995	ACP Broadsheet J Clin Pathol 48:602-610
Management of Massive Blood Loss: a template guideline	Sept 2000	Br J Anaesth. 85(3):487-91.
Management of peri-operative transfusion		www.sign.ac.uk
NICE guidelines on Routine Antenatal anti-D Prophylaxis	May 2002	www.nice.org.uk
Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis	March 1999	Transfusion Medicine 9, 93-97
UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology.	Jun 2000	Gut. 46 Suppl 3-4:III1-III15. www.bsg.org.uk/clinical_prac/ guidelines/man_variceal.htm
Use of anti-D immunoglobulin for Rh prophylaxis	May 2002	RCOG web site – 'Green Top' guideline www.rcog.org.uk/guidelines.asp? PageID=106&GuidelineID=45

101 Things To Do With A Blood Donation – Provision Of Blood For Non-Therapeutic Use

Background

Blood donors give their blood to the NBS on the understanding that it will be used to benefit patients. Usually this means direct transfusion therapy, but a safe supply of blood and blood components is also essential for quality assurance in pathology services, for manufacture of reagents, development of new technologies and the advancement of medical knowledge. The NBS has a policy on the use of donated material, which is consistent with the advice of the Royal College of Pathologists and the Medical Research Council.

Donor consent

Blood donors are provided with information on these 'non-therapeutic' uses of blood, and the donor consent includes provision for their blood to be used in this way, provided that the material is waste or surplus to clinical need (such as buffy coat residues, left-over testing samples or time-expired units), and is anonymised so that it cannot be linked back to the individual donor.

If additional blood samples are needed (e.g. for the establishment of laboratory normal ranges), or if a donation is collected specifically for non-therapeutic use (e.g. for reagent manufacture), then explicit donor consent must be obtained. Results of investigations or research findings may have implications for the donor's health or welfare, and so informed consent is required before any personal identifiable information can be supplied to a third party. Explicit consent is also considered necessary if the donation is to be used for research which is of a sensitive or controversial nature, or if it is to be supplied directly to the commercial sector.

Consideration of requests

Requests for blood come from a variety of sources, including the NBS' own research and development department, NHS pathology laboratories, EQA schemes, universities and research establishments. All requests are considered sympathetically, conscious of the fact that the NBS is the only available source of screened normal blood, however the NBS also has a responsibility to protect the interests of volunteer blood donors.

Applications for donated material for use as the subject of a research project must include details of the research proposal and evidence of peer review and/or approval by a local or multicentre research ethics committee.

The administration of requests is handled by the Hospital Liaison function, however all requests must be considered by an NBS consultant, taking into account both ethical and operational implications. Straightforward requests may be approved at local centre level; all other requests are considered by the NBS Medical Director's management team at their monthly meetings.

The local consultant and Hospital Liaison Manager will discuss the request with other local managers to ensure that it is operationally feasible and will not impact on normal services. They may also discuss it with the relevant NBS Lead Consultant prior to approval, and will liaise with the applicant regarding the most appropriate material for the purpose of the request.

Material suitable for use

The NBS makes increasingly strenuous efforts to minimise waste in its processing and stock management and the availability of 'surplus or waste' material cannot always be guaranteed. If blood stocks become short, the clinical supply will always take priority. However buffy coat residues are always available, and the recent introduction of diversion pouches on blood collection packs means that underweight packs, previously discarded, can now be virally tested and issued for non-clinical use.

Requests for large volumes of blood on a regular basis, e.g. for EQA schemes, present something of a challenge. Some centres have responded by identifying collection sessions at which donors who are ineligible for defined reasons such as travel history may donate specifically for in-vitro use.

Applicants for blood may not always be aware of which component is most suitable for their purposes. We have on occasions supplied material for a trial period so that this can be determined, and NBS consultants are happy to advise.

Cost recovery

Material provided for non-therapeutic use is charged for on a cost-recovery basis. A price list is available on request.

Policy and procedure

A copy of the NBS policy for the supply of donated material for non-therapeutic use may be obtained from any NBS Hospital Liaison Manager or consultant.

Dr Dorothy Stainsby
Head of Clinical Audit
Contact email: *dorothy.stainsby@nbs.nhs.uk*

Frequently Asked Questions (FAQs)

Why doesn't the NBS provide pooled Cryoprecipitate?

The demand for Cryoprecipitate is nationally relatively small, although there are locally higher variations in requests. Its manufacture is, therefore, restricted to only a few NBS centres. The question of pooling this product has been considered in the past, primarily by pooling of finished individual components. This proved a very unsatisfactory procedure as the loss of Cryoprecipitate was significant due to the 'stickiness' of the Cryoprecipitate and the very small volumes involved. Pooling was therefore not pursued further.

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The future of Cryoprecipitate has been very much a concern recently, particularly around the possibility of provision of a pathogen inactivated component. The NBS are pursuing investigations into this area and undertaking work to improve the fibrinogen yield in Cryoprecipitate produced from methylene blue treated FFP. From a component strategy perspective it is believed that Cryoprecipitate is likely to be replaced by a Fibrinogen concentrate in the foreseeable future. No such concentrates are licensed at present, but clinical trials are ongoing.

Given this, the NBS has no current plans to produce pooled cryoprecipitate. Currently resources are being targeted on major safety initiatives, for example, provision of Neonatal components, TRALI and Bacterial Reduction.

Does the NBS consider leucocyte depletion equivalent in safety to CMV serological testing?

Since the NBS implemented universal leucodepletion in 1999, it has continued to test a proportion of its blood components for CMV antibodies and issues these, when requested, for patients considered to be at risk of CMV disease. The literature on pre-storage leucodepletion strongly suggests that it is equivalent in safety to CMV serological testing. This has been endorsed by the Council of Europe, and the American Association of Blood Banks, although not the US Food and Drug Administrative Centre. Some clinicians accept their equivalence but some do not and the NBS has left it to individual Centres to agree with local hospitals what their policy should be.

The only prospective, randomised study comparing the use of leucodepleted and CMV seronegative components was conducted in bone marrow transplant recipients, using bedside filtration (Blood 1995, 86:3598-3603). It was not conclusive in demonstrating equivalence. Bedside filtration cannot be adequately quality controlled and has been shown to be unreliable in providing a guarantee of leucocyte depletion.

A Canadian Consensus Conference (Transfusion 2000, 41:560-569) concluded that serological testing and leucodepletion appeared to be of similar efficacy but was unable to say whether one is definitely better than the other. The benefit of continuing to test after the implementation of universal leucodepletion is unknown and to date there is no published evidence addressing this question. Although a consensus was not reached, the majority of the panel advocated retaining serological testing for most patient groups whilst agreeing that leucodepletion alone provides excellent protection from transfusion-transmitted CMV. There was unanimous agreement that the administration of leucodepleted components should not be delayed if CMV seronegative components are unavailable.

A recent prospective study of bone marrow transplant recipients in the South West treated, between April 1996 and August 1999, with platelets leucodepleted to $<5 \times 10^6$ leucocytes/transfusion and SAG-M suspended, buffy coat depleted CMV seronegative red cells (approximate leucocyte content 10^8/unit) has shown no incidence of CMV in 93 CMV negative bone marrow donor/negative recipient pairs (Pamphilon et al 2002, in press). If similar results can be demonstrated on a larger scale the incremental value of CMV testing could be considered negligible.

In the meantime, the NBS will continue to provide CMV seronegative components when requested for appropriate recipients. In the absence of suitable seronegative components, treatment with leucodepleted components is considered equivalent, with negligible risk for CMV infection, and should not be delayed. The NBS is in the process of reviewing its position on this subject.

NEWS AND SNIPPETS

Handy Hints

Have you any 'Handy Hints' to add to a **Better Blood Transfusion Tool Kit**? We are looking for examples that have made a real difference to blood usage and better blood transfusion that we can share across the whole blood transfusion community.

An example of such a handy hint (taken from article in this edition) could be:

Investigation of every event where blood has been wasted

- All staff involved interviewed
- Clinical incident report completed
- Line Manager / Clinical Director informed
- Incident discussed at the HTC
- Procedures and protocols revised, if necessary

Please send your example to the Editor for possible inclusion in the next edition of *Blood Matters*.

Recombinant Factor VIIa

Since the September issue of *Blood Matters*, in which Denise O'Shaughnessy wrote an article on the potential uses of rFVIIa for inducing haemostasis, an article has appeared in the Lancet, Vol **361**, January 18th 2003, pp201-205, P W Friederich et al, on the use of rFVIIa in patients undergoing retropubic prostatectomy.

Diary Dates

- BBTS Apheresis & Blood Collection SIG Meeting, 2-3 April, Birmingham. [2 April: Therapeutic Apheresis / 3 April: Donor Apheresis and Blood Collection.] *Registration forms by post from*: Medical Secretariat, National Blood Service, Birmingham Centre, Vincent Drive, Edgbaston, Birmingham B15 2DG. Other enquiries to: *carol.mitchell@nbs.nhs.uk* or telephone 0114 2034877
- 4th NATA Symposium on Transfusion Alterntives, 14-15 April, London. Contact email: *congress@nataonline.com* . Website: *www.nataonline.com*
- Royal Society of Medicine in Association with BBTS: The Sensible Use of Blood, 30 April, London. Website: *www.rsm.ac.uk/academ/218-blood.htm*
- Association of Surgeons Annual Scientific Meeting, 7-9 May, Manchester. Website: *www.asgbi.org.uk/*
- ISBT VII Regional European Congress, 3-7 May, Istanbul, Turkey. Website: *www.isbt2003.org*
- Association of Anaesthetists Seminar, 26 June, London. Website: *www.aagbi.org* or telephone Nicola Heard, Educational Events Assistant on 020 7631 8805.

Blood Matters is prepared and issued by the National Blood Service, Oak House, Reeds Crescent, Watford, Herts WD24 4QN (Telephone 01923 486800)
Editorial Board: Dr A Robinson, Dr F Boulton, Dr R Webster, Dr J Harrison, C Hartley, S Penny, A Murray