Summer 2009 • Issue 28

NHS Blood and Transplant

Blood Matters

Information for hospitals served by NHS Blood and Transplant

Inside

EDITORIAL

The passage of time is relentless and it seems that it was only a few moments ago that I sat down to read the editorial that Ruth Warwick had written for the last edition of *Blood Matters*. Once again the editorial team has put together a group of articles on such diverse themes as the usage of fresh frozen plasma, heart transplantation and accreditation of stem cell transplant programmes. With the waning of the age of altruism, our colleagues in donor services have become ever more resourceful in the recruitment and maintenance of blood and blood component donor panels. Here Sue Barnes describes for us recent changes to the blood donor selection guidelines which will allow more older donors as well as those with stable hypertension and diabetics on oral medication to continue to donate blood. The upper age for new donors has, from 15th of December 2008, been extended to their 66th birthday while we now tell donors that they will no longer be retired on their 70th birthday; there is no absolute upper age limit providing that the donor acceptance criteria are met.

Articles on audit feature regularly in *Blood Matters* and this edition is no exception. Janet Birchall and Shuba Allard describe audits of red cell and fresh frozen plasma (FFP) usage respectively and highlight the need for further improvements to practice. In the case of red cell transfusions the treatment of anaemia to avoid unnecessary transfusion is important, whilst FFP continues to be prescribed to patients who are not bleeding and who may have either normal or only minimally abnormal coagulation tests. Dr René de Vries, President of the International Haemovigilance Network, describes for us the purpose of haemovigilance and new developments in the field, in particular the globalisation of haemovigilance.

Following a recent article on battlefield blood transfusion we asked Heidi Doughty to write for us on transfusion practice in trauma patients in the UK and here she describes the changing patterns of blood use in this relatively infrequent but critically important group of patients. Important questions such as the aggressive use of fresh frozen plasma and platelets remain to be answered in good prospective trials. On the subject of platelets, NHSBT has, in recent years, collected an increased proportion of platelets for transfusion by apheresis from component donors. Andy Young, Director of Blood Donation at NHSBT, describes the 80% project and it's works to achieve the specific objective of increasing platelet donations to 201,600 adult therapeutic doses for 2009-2010 (80% of platelets collected). Follow up of the lessons learned in the project will help to ensure that provision of platelets using apheresis donation is both reliable and cost effective.

In November 2008 the two day Transfusion Medicine Update Symposium held at the Royal College of Pathologists included two excellent talks on how to do research by a trainee (Rachel Protheroe) and a professor (David Roberts). Leaving no time for them to gather breath, I immediately asked both presenters whether they would be willing to share their wisdom with the wider audience of *Blood Matters* and I am delighted to say that both articles are featured in this edition. Rachel Protheroe describes the pathway for academic trainees in haematology and transfusion medicine and provides much useful advice for budding researchers who want to follow in her footsteps. David Roberts with his considerable experience of research stresses the importance of cooperation and asking the right questions. Science, he tells us, must continue to push back the boundaries and enable us to comprehend more of the world in which we live; as Immanuel Kant (quoted by David Roberts) said – 'dare to know'!

NEQAS is so much a part of our everyday working lives that most of us either did not know in the first place, or have forgotten that the blood transfusion scheme is 30 years old this year. Clare Milkins describes the evolution of the scheme during that time. Once again we feature articles on transplantation, this time on bleeding and transfusion support in liver transplantation contributed by Louise Powell and Professor Mark Bellamy from the Department of Anaesthesia and Intensive Care in Leeds. They describe how blood requirements have reduced due to improvements in surgery, anaesthesia and advances in transfusion practice. Gareth Parry from Newcastle has written a timely update on cardiac transplantation which now has a 60% survival at 10 years post transplant. His article focuses on tissue type, the use of ventricular assist devices and ends by reminding us of the likely future importance of xenotransplantation.

We live in an increasingly regulated environment and feature two articles covering tissue banking cooperation in Europe and the accreditation of stem cell transplant programmes by JACIE (the acronym is explained in the article). Ruth Warwick explains the different organisations that the tissue banking community interacts with, including the European Union and the directorate responsible for tissue banking activities (SANCO), the European and American Tissue Bank Associations, the World Health Organisation and the International Atomic Energy Authority. The European Commission has funded a project – EUROCET – which is a European Registry for Organ, Tissue and Cell Donation and Transplantation, whilst the EU directorate SANCO supports a project which has allowed the development of requirements for

inspections of tissue facilities – EUSTITE. Stem cell collection and processing facilities are inspected both by the relevant competent authority – in the UK this is the Human Tissue Authority (HTA) – as well as JACIE which also inspects clinical transplant programmes.

In future editions *Blood Matters* will continue to feature regular articles on audit and clinical statistics and we are also starting regular features on tissue banking in different countries (beginning with Spain in the next issue), pioneers of transfusion and tissue banking and finally a series loosely entitled "A day in the life of..." which kicks off in the field of transfusion microbiology. We hope that you will feel that the time spent reading *Blood Matters* was worthwhile for as Benjamin Franklin said 'waste no time, for time is the stuff that life is made of', whilst on a more sceptical note Douglas Adams reminded us that 'Time is an illusion – lunchtime doubly so'. Happy reading!

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Recent Changes to Blood Donor Selection Guidelines

There have been significant changes to the Donor Selection Guidelines (DSG) implemented and about to be implemented in NHSBT this year. The purpose of this article is to review how and why these changes were made.

Since 1st September 2008 we have accepted donors with stable treated hypertension as whole blood and component donors, regardless of the anti-hypertensive medication being taken, provided it has not been changed within the four weeks before donation, and the donor has no history suggestive of cardiovascular or cerebrovascular disease, renal impairment or peripheral vascular disease. We allow donors to self-report that their hypertension is well controlled. At the same time we started to allow individuals with diabetes on oral medication to be donors, with similar provisions. The Blood Safety and Quality Regulations 2005 require permanent exclusion of diabetics if being treated with insulin.

The DSG is published by JPAC (the Joint Professional Advisory Committee of the UK Blood Transfusion Services and the National Institute of Biological Standards and Control). Their decision to review the guidelines on donors with stable treated hypertension and diabetes on oral medication was made because these are common in the population eligible to donate blood. About 1.5% of the population at age 40 and 16% at age 70 are on treatment for hypertension. The prevalence of both conditions is increasing, in part because of increasing obesity in the general population. Donor deferral data, though of limited usefulness, suggests that hypertension is a frequent reason for deferral with 3,960 donors deferred for this reason between July 2006 and June 2007 (2.1% of all deferrals). This data needs to be interpreted with caution as it does not include donors previously permanently deferred, or those who self-defer.

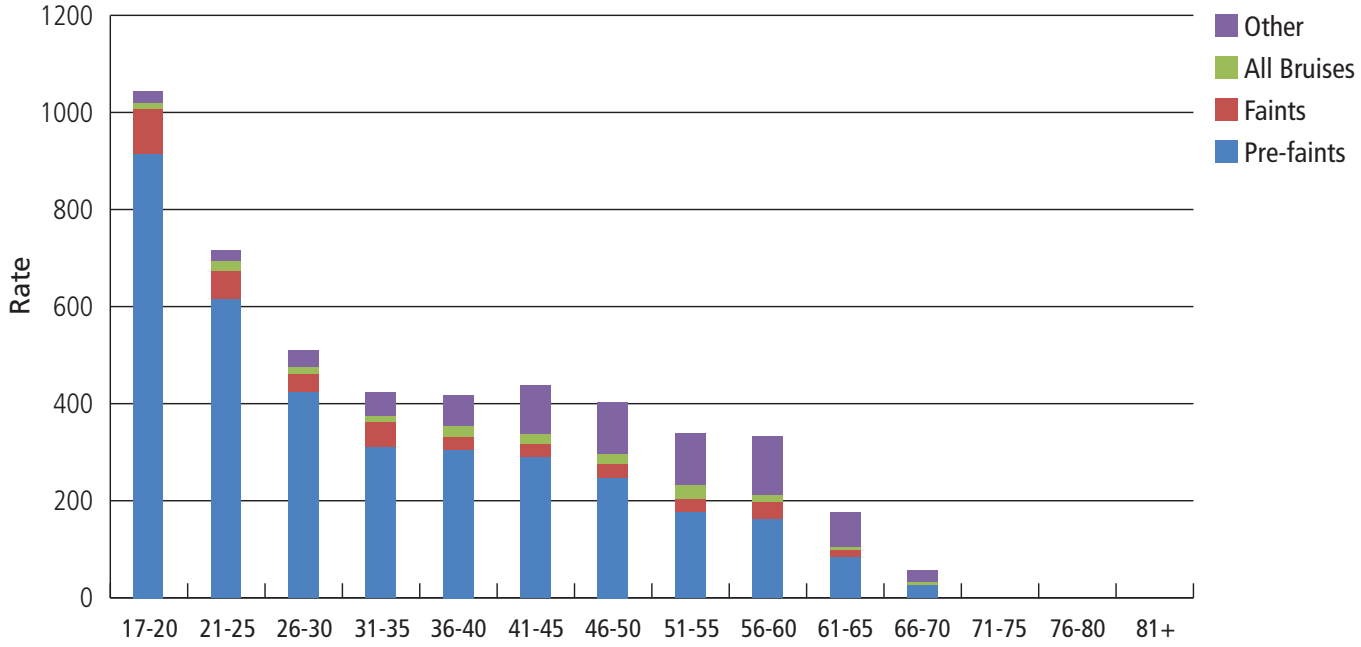
Other blood services accept donors with these conditions and a systematic literature review suggested that acceptance of such donors is safe. A review of the records of NHSBT donors with diet-controlled diabetes (previously accepted) showed no excess of adverse reactions, although the prevalence of autonomic neuropathy in longstanding diabetes might suggest a higher risk of adverse reactions.

Donating Blood at one of the NHSBT local sessions

Obviously recipients' safety has to be assured. Expert advice was sought as to the possible risks to the recipient of blood as a direct effect of medication in the blood and any possible teratogenic effect of medication transfused to a pregnant female. A unit of whole blood from a donor taking oral medication might contain 10-100 fold less than a single therapeutic dose and is very unlikely to produce hypoglycaemia or hypotension in the recipient. The experts were not specifically asked to consider the risk to a neonate. However the acceptance criteria for US plasma donors include anti-hypertensive medication and oral medication for diabetes, thus the UK blood services are already using plasma from donors taking these drugs for treatment and transfusion to neonates and children up to 16 years.

There is a theoretical risk of fetal abnormality if blood containing a teratogenic drug is given to a woman in early pregnancy. The view taken was that, in terms of likelihood and impact, the risk of producing a fetal abnormality is far outweighed by the risk of jeopardising the supply. Currently a small number of drugs are specifically excluded by the DSG because of concerns

Event rate per 10,000 donations by age group



regarding fetal abnormality. However donors taking other known or likely teratogens are currently accepted e.g. Statins. Available data on the use of blood in pregnancy is limited, however data from the EaSTR Study (*Blood Matters* Spring 2007) suggests that <0.1% of red cells are given to pregnant women before the peripartum period, and the 2007 Health Service Circular *Better Blood Transfusion: Safe and Appropriate use of Blood,* strongly advises avoiding transfusion in pregnancy unless absolutely necessary.

In 2005 JPAC issued a change to the DSG to allow recruitment of new donors up to their 66th birthday and to allow regular and returning donors to continue to donate until their 70th birthday. On 1st July 2008 NHSBT implemented this change. On 15th December 2008 we stopped retiring regular donors on their 70th birthday, with no absolute upper age limit, provided that they meet UK Blood Services' donor acceptance criteria as assessed by routine procedures. We will not require any additional pre-donation screening or clinical observations for elderly donors.

The age criteria were examined because whilst the Age Discrimination Act 2006 does not apply to volunteers, it has focussed attention on ageism, An arbitrary upper age limit for blood donation is increasingly hard to justify and complaints received by the National Blood Services indicate that there is a considerable degree of donor dissatisfaction with the obligatory upper age limit. Life expectancy is increasing, and it is predicted that the population aged 65-74 and >75 will increase by 43% and 76% respectively in the 25 years from 2006. Currently NSHBT retires between 8,000 and 10,000 donors per year and this will increase as the post-war population 'bulge' reaches 70 plus. A study of NHSBT donor adverse events shows that events become less common with increasing donor age.

Information regarding other blood services' upper age limit for donation was sought; two blood services have documented experience of elderly donors. The Canadian Blood Services have only recently removed the upper age limit. The American Red Cross has long experience of elderly donors; the upper age limit for blood donation was abolished by the FDA in the 1980's, and has recently initiated a comprehensive haemovigilance programme including complications of blood donation. Their analysis of donor adverse events in 2006 provides compelling evidence of the safety of whole blood and apheresis donation by elderly donors. A literature review was undertaken; the majority of publications come from the US and showed no excess of adverse reactions in older donors although a slight increase in bruising has been noted in some series.

The value of routine external medical referral was assessed by the Canadian Blood Services. Following referral to the family physician, 18/862 (2%) of prospective donors were deferred. Thus JPAC will not require screening of the older regular donor beyond that which is routine for all donors.

Full details of the new recommendations can be found on the JPAC website: www.transfusionguidelines.org.uk

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Acknowledgements

Dr D Stainsby, and Dr M Butler.

Audit of Red Cell Use in Hospitals in the South West and West Midlands Regions

Introduction

Since the introduction of the Serious Hazards of Transfusion initiative in 1996 there has been a heightened awareness that blood transfusion can cause harm. This appreciation of risk, in addition to the increasing cost of processing blood, reduced blood donor availability and as a consequence threat of blood shortage, resulted in an 18% reduction in red cell demand between 2000/01 and 2007/08. An audit carried out in 2005 in hospitals in Northern Ireland suggested that 20% of red cell transfusions were inappropriate. Since this audit there has been little information on the appropriateness of red cell transfusion practice and therefore the South West and West Midlands Regional Transfusion Committees (RTCs), supported by the National Comparative Audit group, agreed to audit red cell use in their hospitals.

Method

The information requested was designed to be available from computer records alone. Patient symptoms, which are often subjective, variably recorded and would have necessitated note searching, were not included. Patient age, hospital specialty and the number of units transfused were requested for all transfusion episodes over a one week period and more detailed information to determine appropriateness was requested for the first 40 episodes only. A questionnaire requesting information on red cell transfusion guidelines was sent to Consultant Haematologists with responsibility for transfusion and the National Blood Transfusion Committee (NBTC) "Indication codes for transfusion: an audit tool" were used as the basis to define appropriateness.

Results

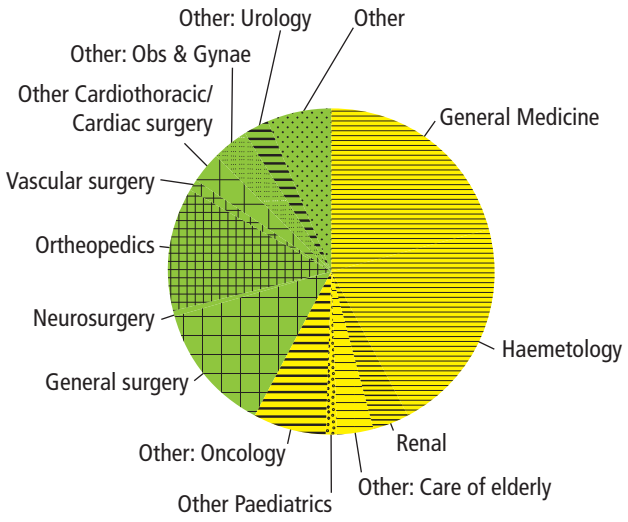
The audit took place in September 2007. Overall participation was 46% (26 of 56 hospitals) but improved to 66% (20 of 30 hospitals) when only hospitals with an annual red cell order of more than 5,000 red cell units were considered.

Transfusion threshold guidelines were usually in keeping with NBTC recommendations including patients with acute blood loss due to gastrointestinal bleeding despite guidelines from the British Society of Gastroenterology, which advise a higher threshold of 10 g/dl should be used. In each of the transfusion categories for which a transfusion threshold was requested 10-35% of replies stated that no haemoglobin value was used.

A total of 1,113 red cell transfusion episodes were audited. The frequency of transfusion increased up to age 80 years, with less than one third of all transfusion episodes occurring in patients under 65 years of age. 57% of all episodes occurred in medical rather than surgical specialties. (See chart below)

More detailed information was available for 822 transfusion episodes and results for this group were as follows – chronic anaemia was stated as a reason for transfusion in 43% of cases and bleeding in 42%. 10% were associated with a mean cell volume of greater than 100fl and 14% with a mean cell haemoglobin of less than 27pg. Fewer than 40% of cases in each of these groups with abnormal red cell indices had haematinic investigations performed. 60% of surgical patients were anaemic on admission. 80% of all transfusion episodes were considered appropriate, 19% inappropriate and 1% indeterminate.

Transfusion episodes per speciality



Medical specialties are coloured yellow and surgical specialties green

Discussion

The main aims of this audit were to understand current red cell transfusion practice and identify whether further reductions in red cell use are possible. By chance, this was performed in September 2007, which corresponds to the time red cell issues stabilised if not increased. This audit is therefore well placed to provide useful data on current use.

Elderly patients were more frequently transfused and most transfusions were in medical specialties. These results have clear implications for future blood supply as the age of the population is steadily increasing and

medical conditions are not subject to reduction of blood use by better surgical technique or autologous transfusion.

Perhaps one of the most remarkable results in this audit was the fact that around 60% of all patients who were transfused and underwent surgery were anaemic on admission. Many of these may respond to treatment other than blood transfusion, and pre-operative assessment to identify, investigate and treat anaemia must be a priority. The assessment of red cell indices in this audit also indicates that haematinic investigations would be of benefit across all specialties.

An important aim of this audit was to try and assess the appropriateness of transfusion and for this purpose NBTC guideline haemoglobin values were mainly used. These levels were much less tolerant than those used in the audit performed in Northern Ireland in 2005. In the latter the threshold haemoglobin for all patients with bleeding, marrow failure, receiving chemotherapy and/or radiotherapy or with symptoms of anaemia was below 10g/dl. Despite these differences, the results were almost identical with about 80% of all transfusion episodes appropriate.

The audit of transfusion guidelines identified that the majority of hospitals supported the use of haemoglobin thresholds suggested by the NBTC. Several hospitals however stated that no haemoglobin levels were used to help decide when transfusion should occur. Given that symptoms and signs of anaemia are usually non-specific, appropriate transfusion practice is likely to be improved by consideration of haemoglobin threshold levels.

In summary transfusion practice in this audit was commendable, however further improvement remains possible. Each transfusion episode should continue to be considered for appropriateness but more effort is now required to treat anaemia in both medical and surgical patients to avoid the need for transfusion. Prior to this audit the West Midlands RTC had already identified methods to detect and manage anaemia preoperatively which is available from:
www.transfusionguidelines.org.uk/docs/pdfs/rtc-wmids_edu_anaemia_guide_preop_07_11.pdf

Since release of this audit the NBTC guidelines have been updated and the South West RTC plans to encourage use of this document in transfusion laboratories to help staff question requests where the reason for transfusion is unclear.

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2. Clinical Resource and Efficiency Support Team (CREST), Department of Health NI – Regional Appropriateness of Blood Transfusion Audit, NI Regional Transfusion Committee 2006.
3. National Blood Transfusion Committee "Indication codes for transfusion: an audit tool" www.transfusionguidelines.org.uk

National Comparative Audit of the Use of Fresh Frozen Plasma in Adults

Background

Fresh Frozen Plasma (FFP) may be associated with a high rate of inappropriate transfusions, with some studies indicating rates of up to 50% non compliance with established guidelines. FFP transfusions are not without risk and indeed may carry the highest risk of all blood components in relation to transfusion reactions. Accordingly a national comparative audit of the clinical use of FFP against standards derived from the BCSH guidelines was undertaken with a view to reviewing current practice.

Methods

All NHS Trusts, NHS Treatment Centres and Independent Hospitals in England were invited to participate in the audit. The target sample for each participating centre was 40 consecutive patients receiving FFP, or if less than 40 cases likely, then all patients within a three month period (April to June 2008). All patients, regardless of age or gender, were eligible for inclusion. Centres were also asked to complete an organisational audit questionnaire.

Results

General

In total, 309 centres across England were approached for participation in this audit. The response rate was 75% (186/248) from NHS hospitals and 16% (10/61) from Independent Hospitals.

Of centres responding to the organisational questionnaire, 80% (145/182) reported the existence of

guidelines for FFP use in adults and 57% (104/182) reported the existence of guidelines for paediatric use. 90% (162/182) of centres stated that they had guidelines for the management of massive haemorrhage. 88% (160/182) stated that they used methylene blue treated FFP for children <16yrs and six stated that they used only solvent detergent treated plasma in this patient group.

183 centres (178 NHS and five Independent) provided clinical data on 5,032 FFP transfusion events for analysis in this audit. 63 cases receiving FFP in conjunction with plasma exchange were excluded from further analysis. The remaining 4,969 transfusion events comprised 4,635 (93.3%) in patients aged 16 years or over, 114 (2.3%) in children aged 1-15 years and 220 (4.4%) in infants aged less than one year.

FFP use in adults aged ≥ 16yrs

FFP transfusions were most frequently given to adults in theatres/recovery (23%), or Intensive Treatment Unit/ High Dependency Units (32%), or on medical wards (22%). The indication for transfusion was not documented in the notes in 28% of all adults.

The more common clinical groups for FFP use in this age group were warfarin reversal, liver disease and surgery (including cardiac). As shown in Figure 1, 44% of all FFP transfusions were given to adult patients in the absence of documented bleeding. For 12% of cases the main reason for giving FFP was to manage abnormal coagulation. Of those cases given FFP transfusions before or during invasive procedures/surgery, the more common indications were surgery including laparotomy (17%), cardiac surgery (8%), endoscopy (7%) and central line insertion/removal (15%). It should be noted that in the 56% of patients given FFP for bleeding, it was not possible to differentiate between minor or more severe grades of bleeding in this audit.

Use of FFP for warfarin reversal

BCSH guidelines on administration of FFP and on oral anticoagulation state that the reversal of anticoagulation in patients with major bleeding requires administration of a prothrombin complex concentrate. FFP has only a partial effect, is not the optimal treatment and should never be used for the reversal of warfarin over-anticoagulation in the absence of severe bleeding. 14% of all FFP transfusions given to adults were for warfarin reversal. Of these, 56% were given to patients who were not bleeding.

Dose of FFP given

A standard FFP dose is at least 10-15ml/kg, although this may be exceeded in massive haemorrhage. There was wide variation in the dose of FFP transfused by weight. The median overall dose in adults was 11ml/kg. In 40% of adults the dose was less than 10ml/kg.

The use of coagulation screening tests (PT or INR)

8% of adults did not have INR or PT reported before FFP was given. Following FFP transfusion, hospitals were unable to provide coagulation results for 14% of adults. 27% of adults without bleeding who received FFP transfusions and who had INR tested had INR <1.5. Similar proportions at 23% without bleeding and with PT tested had PT <16 seconds.

Changes in PT and INR after FFP administration

The effect of FFP, as recorded by the difference between the first recorded post-transfusion INR or PT result and the pre transfusion result was small in the majority of cases. When results for all adults were evaluated, the median reduction in INR was -0.2 (inter-quartile range -0.7 to 0; n=2543) and the median reduction in prothrombin time was -1.9 seconds (inter-quartile range -5.9 to 0.1; n=2701). As might be anticipated, the median reductions in INR or PT were more apparent for cases where the pre-FFP transfusion INR or PT was more elevated. The median reduction in INR was -0.0 for 985 cases with pre-transfusion INR 1 – 1.5, was -0.3 for 1,080 cases with pre-transfusion INR 1.6 – 2.9, and was -1.8 for 272 cases with pre-transfusion INR 3 – 4.9.

Additional keys points from Paediatric data

Most FFP transfusions to children aged 1-15yrs were given in theatres/recovery (35%) or in paediatric intensive care units (33%). In this age group 48% of all FFP transfusions were given in the absence of any documented bleeding.

Most FFP transfusions to infants aged <1yr were given in neonatal/paediatric intensive care units (60%) or theatres (14%). In infants 62% of FFP transfusions were given in the absence of documented bleeding. Only 32% of hospitals treating paediatric patients (56/176) stated that they used specific reference ranges for the neonatal age group.

Discussion; so what?

The aim of this audit was to evaluate use of FFP by comparison to current BCSH guidelines. One of the main findings from the audit was the high proportion of FFP use for patients without documented bleeding. Many non-bleeding patients continue to receive FFP with only minor derangements of their PT or INR or even with normal coagulation results. The findings also indicate that use of FFP results in only minimal or no improvement in PT or INR. These findings raise important questions around cost and risk implications and the effective use of

FFP transfusion, although only high quality trials with clinical outcomes will address the issue of which patients really benefit from FFP administration.

It is hoped that the audit has supported the collection of sufficient credible data from a large and representative sample of hospitals to begin an informed dialogue across hospitals and the NHS Blood and Transplant in England to lead to meaningful multidisciplinary discussion on the appropriate (and inappropriate) use of FFP.

Examples of initiatives to address the inappropriate use of FFP might include empowering transfusion laboratory staff to question medical staff about the right dose, or the use of FFP where there is no clear clinical indication for its use in patients without evident bleeding. FFP also continues to be used for reversal of warfarin over-anticoagulation and in many patients without bleeding, which raises important issues about the availability and use of policies on the appropriate use of vitamin K and prothrombin complex concentrates. The widespread use of FFP for prophylaxis in non bleeding patients now requires careful scrutiny.

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Acknowledgements

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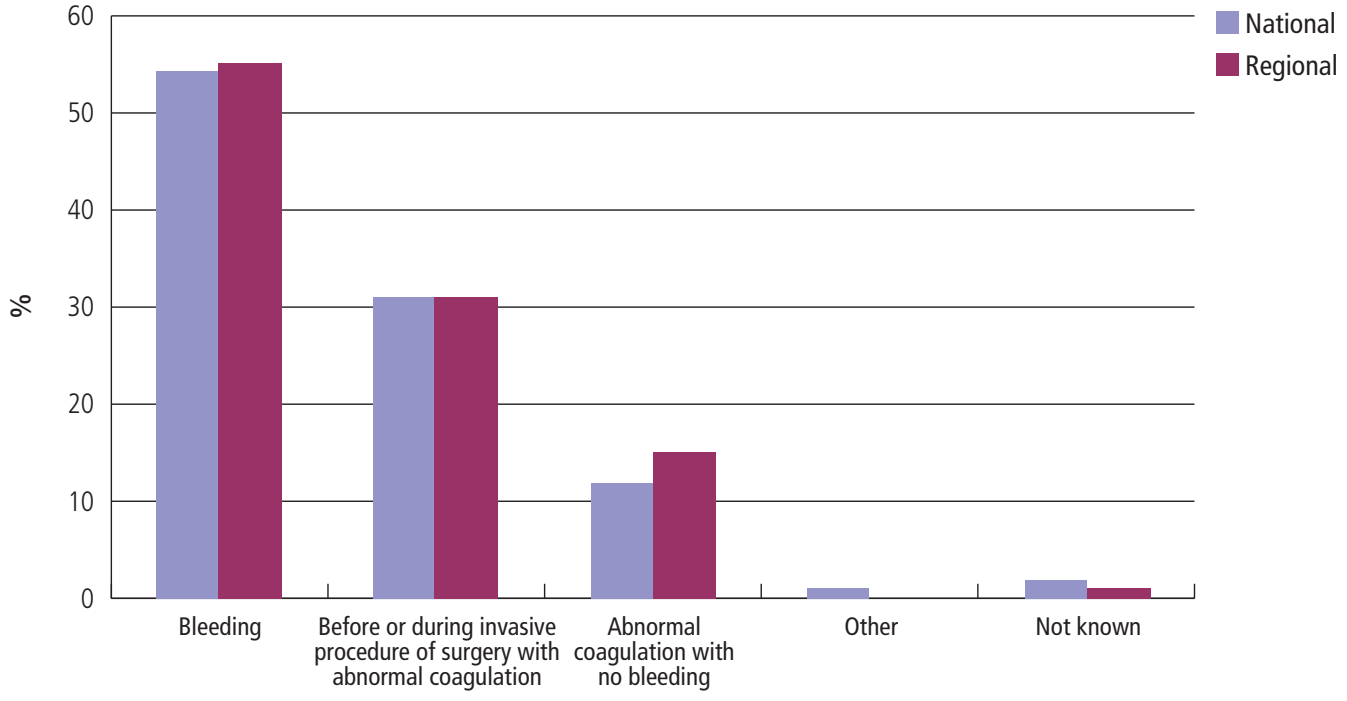
Figure 1: Main reason for FFP transfusion in adults. The slide shows the national data and also example data from one of the 10 regions emphasising the comparative nature of the audit



Haemovigilance: A Safe Investment

Introduction

Haemovigilance is the surveillance of the whole blood transfusion chain (from patient to donor and back) with the main purpose to collect and assess information on undesirable effects of labile blood products and with the goal to improve the safety of blood transfusion.

Triggered by the HIV scandal, the first surveillance system for blood transfusion was initiated in France in 1994. Soon after other European countries followed this initiative, led by the UK where SHOT was launched in 1996. Presently almost all EU countries have established a Haemovigilance System and the number of Haemovigilance Systems outside Europe is steadily increasing.

In 1997 the European Haemovigilance Network (EHN) was founded with the aim of increasing the safety of clinical blood transfusion medicine in Europe. Members of the Network are (national) Haemovigilance Systems represented by an official contact person. The Network started with five and has grown to over 25 members including some non-European haemovigilance systems. The main objectives are:

- to facilitate exchange of information between the members,
- to encourage joint activities and
- to undertake educational activities in relation to haemovigilance.

To this purpose the following activities were undertaken:

- a website (www.ehn-org.net) was developed and maintained.
- the organisation of annual meetings of the official contact persons of the members and other participants actively involved in activities of the EHN.
- to address important issues in separate Working Parties and last but not least:
- The organisation of annual seminars on haemovigilance in different European countries. These seminars have been a big success. The last Seminar, the 11th European Haemovigilance Seminar in Rome, was attended by 265 participants from 34 different countries (including many from outside Europe).

Results

Probably the most important result of haemovigilance has been that it has shown that since the mid nineties blood transfusion in Europe is quite safe and notably that blood components are extremely safe compared with other interventions and products in health care.

The majority of the serious adverse reactions and events that do occur happen in the hospital part of the blood transfusion chain. Particularly the data from the UK Haemovigilance System SHOT have drawn attention to the fact that about 50% of these are due to administrative errors and the corrective measures instituted subsequently have resulted in a further increase of the safety of clinical blood transfusion in the hospital.

Well functioning haemovigilance systems, such as **AFSSAPS** (Agence Francaise de Sécurité Sanitaire des Produits de Santé) in France, **SHOT** (Serious Hazards Of Transfusion) in the UK and **TRIP** (Transfusion Reactions in Patients) in The Netherlands have documented the success of various measures to even further improve the safety of blood products. Two examples: the deviation pouch applied during blood drawing from a blood donor in order to minimise the risk of contaminating skin bacteria and the decision to use only plasma from male donors have been demonstrated to result in significant decreases of serious adverse reactions due to respectively bacterial contamination of blood products (particularly platelets) and TRALI (Transfusion Related Acute Lung Injury) reactions.

The results of many activities of the EHN such as the contribution to the high quality of haemovigilance in Europe through digital information exchange, meetings and seminars is difficult to measure but are certainly important.

Concrete results include the standardisation of definitions and reporting of adverse reactions in patients and donors, both in collaboration with the ISBT Working Party for Haemovigilance. See www.ehn-org.net/public library/ISBT documents.

Developments

Three new developments in haemovigilance are expected that will have an impact in the coming five years.

The first is a ***globalization of haemovigilance.***

Haemovigilance started and grew up in Europe. However countries such as Canada and Japan have well functioning Haemovigilance Systems and it is clear that the interest in haemovigilance is growing also outside Europe.

Therefore the Board of the EHN has recently decided to become an official international network and to change the name into International Haemovigilance Network (IHN).

The second is that ***haemovigilance has to deal with more than the safety of blood transfusion alone.*** Haemovigilance should become part of a quality system of the blood transfusion chain. Thus far, focus was put on the surveillance of the safety of blood transfusion and on measures to improve this. Data from an anaesthesiology survey in France indicate however that many more peri-operative deaths are due to under-transfusion or delayed transfusion than to adverse reactions of transfusions given in time. Also the safety of measures that are often proposed to stimulate blood saving strategies (e.g. cell savers) and medicinal products (e.g. anti-fibrinolytics) will have to be taken into account. Presently we do not know enough about the safety of these alternatives to be sure when to advise their use.

Another issue is optimal blood usage. The awareness that apart from vital indications the efficacy of blood transfusions is often unknown or not established or even negative has resulted in a significant reduction of the use of blood products as documented by many Haemovigilance Systems. One step further would be the surveillance of appropriate or optimal blood use in a more detailed way, e.g. through the collection of a set of indicators which may be provided easily by most hospital information systems.

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Resources

1. EHN, The European Haemovigilance Network: www.ehn-org.net
2. AFSSAPS, to which the French Haemovigilance System belongs: www.afssaps.sante.fr
3. SHOT, the Haemovigilance System of the UK: www.shotuk.org
4. ISBT Working Party for Haemovigilance: www.ISBT-web.org/documentation
5. TRIP, The Dutch Haemovigilance System: www.tripnet.nl

Transfusion Support for Trauma

Trauma causes significant morbidity and mortality and accounts for 1 in 10 deaths worldwide. The NCEPOD 2007 'Trauma: who cares' states that there are approximately 240 severe cases of trauma each week, in the UK of which half are due to road traffic accidents. It is estimated that bleeding accounts for 39% of trauma related deaths, some of which are potentially preventable. Emergency care is directed to the prevention of injury related death and disability. Stopping the bleeding is essential to saving life. Blood components may save life during the initial resuscitation as well as play a major role in the secondary prevention of death and disability.

Changing blood use in trauma care

Most trauma care is for mild and moderate injuries. These injuries do not require blood components. Only about 2% of casualties require more than 10 units of blood i.e. massive transfusion. Practice is changing in the use of the transfusion for trauma. For more than 20 years, civilian and military practitioners have based their resuscitation strategy on ATLS principles. Initial resuscitation advised fluids followed by blood. Current opinion suggests that aggressive fluid volume administration in the context of uncontrolled haemorrhage may exacerbate bleeding and increase mortality. This is due to a combination of both haemodilution and 'popping the clot' by increasing the blood pressure. It is increasingly recognised that a significant percentage present with abnormal coagulation tests. A number of authors have demonstrated that approximately a third of all patients with an injury severity score (ISS) of greater than 16 have an acute coagulopathy. The coagulopathy is directly proportional to the severity of the injury and is also an independent indicator of mortality. The cause of the coagulopathy is multifactorial. It is more than haemodilution and includes consumption of both coagulation factors and platelets; increased fibrinolysis; impaired function of platelets and coagulation factors, metabolic acidosis, hypothermia and hypocalcemia. The early management of these patients requires the management of both the haemorrhage and prevention of the coagulopathy. Emerging practice requires the early and aggressive use of blood components and is increasingly being referred to as haemostatic resuscitation.

Haemostatic resuscitation

Haemostatic resuscitation suggests the use of a balanced and physiological mix of blood components. In the first place, this requires the early use of plasma in a

1:1 ratio with packed red cells. This concept developed as a way of treating massively injured patients seen in the combat support hospital in Baghdad, where it appeared to markedly reduce coagulopathic bleeding. A retrospective review of this experience showed that the equal use of plasma to red cells was associated with a reduction in mortality from 66% to 19%. Civilian trauma centres have confirmed this pattern of improvement in retrospective reviews of their own experience. Although the optimal proportions of blood and plasma have yet to be determined, it is increasing accepted that severely injured trauma patients should be resuscitated from the outset with a mix of the red cells and plasma. The use of platelets is less clear. Work has showed that the use of platelets in addition to plasma further reduces the risk of coagulopathy and mortality. The early use of plasma reduces the risk of dilutional hypofibrinogenaemia and therefore the need for fibrinogen replacement. However, there is evidence that increasing plasma fibrinogen concentration leads to denser and stronger clots. The target for fibrinogen treatment may be nearer to 2g/dl rather that 1g/dl. The options in the UK for fibrinogen replacement are cryoprecipitate and fibrinogen concentrate. The latter is currently used on a named patient basis. The role of routine anti-fibrinolytics is unclear. Haemostatic resuscitation forms part of wider resuscitative measures which include early damage control surgery focused on the stabilization of vital physiology.

Massive haemorrhage protocols

Patients with catastrophic uncontrolled haemorrhage may require massive volumes of blood components. Such a surge in demand places an enormous strain on the hospital transfusion laboratory. Junior staff may not be familiar with the use and dosage of blood components. Massive haemorrhage protocols provide a pre-determined management framework for both clinical and laboratory teams. The use of protocols should facilitate the rapid provision of a fixed formula physiological mix of components. The initial use of components may be without monitoring. However, monitoring should then be used to allow for target directed therapy aiming for physiological and laboratory parameters. Universal blood groups may be used in 'SHOCK PACKS' but group specific components should be used wherever possible to reduce the burden on blood stocks. All trusts with emergency departments should develop their own massive haemorrhage protocol. The protocol will be defined by the geography, staffing and practices of the trust. The protocol should address the following options:

- Activation of the protocol including identification of the patient at risk.
- Calling in additional BMS staff.
- Co-ordination and communication.
- Sample and component transport.
- The early provision of liquid plasma and red cells.
- The early use of group specific components.
- Access to platelets and cryoprecipitate.
- Use of laboratory and point of care testing.
- Standown.

Laboratory procedures

The impact of such protocols on the laboratory should not be underestimated. Existing processes and procedures may require re-engineering. Change management should conform with MHRA standards. Laboratory information systems should be adjusted as required to release un-cross matched components with compatibility forms. Bulk-thawing may be both time-consuming and messy. Transport and temporary storage must maintain the appropriate temperatures. Procedures should include the need for early re-supply from the blood service. All areas should maintain activity logs for subsequent review. Traditionally, laboratory results were required before component release. The common laboratory tests used are the haemoglobin or haematocrit, platelet count, prothrombin time, partial thromboplastin time, and fibrinogen concentration. These tests are widely available reproducible and cheap, but may place a significant burden on the single-handed BMS who is busy providing blood components. Thromboelastometry has traditionally been used to monitor coagulation function in major surgery but was considered to be too slow and costly for trauma. Newer versions appear to be faster and to provide useful point of care monitoring but must be subject to a quality management system.

Transfusion safety

Blood transfusion is not without risks. The use should always be appropriate even during the acute phase of resuscitation in order to reduce donor exposure. Not all major haemorrhage requires a high use of plasma. It is only those at risk of coagulopathy. The challenge is identifying the patients at risk and restoring homeostasis including support of oxygenation, perfusion and body temperature. For all trauma cases, control of bleeding will reduce the need for donor blood. The use of tourniquets is returning to civilian practice and there is adoption of a wide variety of techniques used not only by the military but also by practitioners of complex surgery. Early transfer to emergency surgery should provide definitive control of surgical bleeding. Intra-operative cell salvage will provide recovered red cells but may require additional plasma and platelets to maintain adequate haemostasis. Donor exposure can be reduced by the use of apheresis platelets and by avoiding the use of cryoprecipitate. Products such as fibrinogen and PCCs increase donor exposure but reduces other potential infectious risks.

Reducing risks

The biggest risk of transfusion is ABO mismatches associated with failures of identification and specimen labelling. Attention to detail is important despite the difficult situation. Maintaining transfusion records may be difficult during the fast moving phase of active resuscitation but full reconciliation of blood components is required after the event. Documentation must be complete in order to ensure full traceability i.e. all components issued must be accounted for either as transfused to the patient or returned to the laboratory. Trauma patients often require repeat surgery. Massive transfusion may be complicated by allo-immunisation. Fresh samples should be taken every two days during the active post trauma surgical phase in order to screen for atypical antibodies and reduce the risk of haemolytic transfusion reactions.

Summary

Only 2% of the civilian trauma patients are likely to require massive transfusion. For most centres in the UK, this will be relatively infrequent, and therefore requires a pre-agreed and practiced protocol. Such a protocol will allow the clinical and laboratory teams to provide appropriate timely transfusion support. However, many questions remain regarding the best transfusion practice for trauma. In particular, is there a role for the aggressive use of fresh frozen plasma and platelets in civilian trauma patients? The question is an important one and demands to be tested in a well designed prospective, randomized controlled trial.

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Platelet Donation – the 80% Project Mission Impossible?

Many hospital patients are in special need of platelet transfusions. Some patients are unable to make sufficient platelets in their bone marrow to prevent or stop bleeding. Others, such as those with severe infections or those who are undergoing major surgery, may require platelet transfusions as a result of blood loss or through destruction as a result of the disease process. A side-effect of chemotherapy is impaired platelet production.

Donating Platelets at Brentwood Donor Centre

How are platelets collected?

At present, platelets are collected from donors in two ways – directly from Component Donation (CD), as well as by extraction from Whole Blood Donations (WBD). In CD the donor is attached to a cell separator which extracts specific blood components (platelets, red cells or plasma) and returns the remainder to the donor. The advantage of this is a single donor source rather than a pooled source of platelets, and the establishment of a panel of dedicated platelet donors who can donate more frequently.

What was the challenge?

At March 2008, approximately 60% of all platelets collected nationally were from CD. Increasing the percentage of CD platelets has the theoretical advantage of reducing the risk of vCJD transmission to patients. On average one CD platelet donor produces 2 Adult Therapeutic Doses (ATD) of platelets from each procedure. To produce the same amount of platelets from pooled buffy coats requires 8 donations of the same blood group. Thus by using CD rather than pooling, the risk of vCJD transmission may be reduced.

The Project – Mission Possible?

The overall objective of the project was to increase the number and proportion of platelet donations by CD to 80% of issues to hospitals by April 2009 as part of a Department of Health strategy to reduce risks and improve patient safety.

The specific objectives are:

1. To increase platelet collections to 201,600 ATDs for 2009/10 from 148,058 in 07/08.
2. To collect platelets by blood group according to agreed targets at each centre by April 2009.

Progress – How have we done?

The ATD targets were achieved before the end of March 2009. The focus is now on maintaining the level of collections both overall and by blood group through the next year. The main activity that has given rise to increased collections has been intensive recruitment of platelet donors from amongst whole blood donors. Staff at the donor centres and on mobile collection teams have been responsible for this, in conjunction with large-scale central mailings to existing whole blood donors, followed up by telephone calls from the National Contact Centre.

Platelet donors are currently drawn from whole blood donors. As well as being required to frequently attend one of the centres, whole blood donors are only eligible to become platelet donors if they have a platelet count which will yield a minimum of two adult therapeutic doses per donation within the prescribed time of 90 minutes. All recently recruited platelet donors have been male. New tests to detect anti-leucocyte antibodies which may be present in female donors following pregnancy are now available to facilitate recruitment from April onwards.

Specifically, the impact across the donor centres between December 2008 and March 2009 can be measured by:

- Over 11,200 samples have been taken from potential platelet donors at the centres and at local mobile collection team sessions (December – March).
- Over 5,500 donors (nearly 50%) have met the criteria to donate platelets.
- Over 3,000 new platelet donors have already booked an appointment for their first donation.
- 1,810 donors have successfully made their first platelet donation.

This work has made a significant impact on the size of the platelet donor panel. Between October 2008 and February 2009 the number increased by over 20% from 9,400 donors to 11,300 donors. Because of the continuing work at all of the 24 Donor Centres across England further increases are anticipated during 2009.

What does the future hold? – Current and future initiatives

The project team is currently planning and working on implementing a smooth transition from project involvement in the donor centres to full operational management, ensuring that all of the initiatives that have been implemented continue to be used and their effectiveness maintained throughout 2009.

A number of concurrent initiatives are under way to maintain the level of CD platelet donors at 80% and increase it further. They include:

a) further mailings to whole blood donors.

b) a review of donor centre opening hours.

c) the implementation of HLA antibody testing, to enable recruitment of female platelet donors.

d) the recruitment of platelet donors direct from the community, rather than via the whole blood route.

e) machine validations to 'turn up' collection productivity on current machines.

f) increasing platelet donor productivity, by encouraging more frequent attendance (10 times a year), enhanced panel management booking appointments on session, and acquiring a greater yield at each procedure ('triple doses').

g) reviewing CD satisfaction to reduce donor attrition and lapsing behaviour.

h) aligning staff and resource to where collection potential exists.

i) work towards daily targets by blood group for individual donor centres, to maintain supply continuity.

j) agreeing an action plan for each donor centre to meet targets for collections, blood group mix, donor recruitment, donation frequency, donation productivity, capacity utilisation and product quality.

k) decreasing wastage by readjusting component collection by blood group by processing centre to reduce import/export inefficiencies caused by imbalances of collection.

In essence the project has been very successful in working towards its objectives with tremendous strides forward to achieve 80% week on week. Consolidation of the lessons learnt and adoption of the key initiatives will help ensure that provision of platelets by CD is reliable and cost effective, leading the way forward to any potential increases in requirements that might be forthcoming. Well done to all concerned.

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How I do Research: A Trainee's Perspective

Research in Haematology and Transfusion Medicine has a long and distinguished record in the United Kingdom, encompassing basic science and translational research. However, in the last decade there has been a 25% reduction in the number of academics and a worrying trend towards providing fewer opportunities to pursue research during Haematology and Transfusion Medicine training programmes. The decision to undertake research as a trainee can sometimes be daunting one and the resulting financial, social and clinical training impact considerable. Trainees need to address the questions of why, when, where and how to do research.

Why do research?

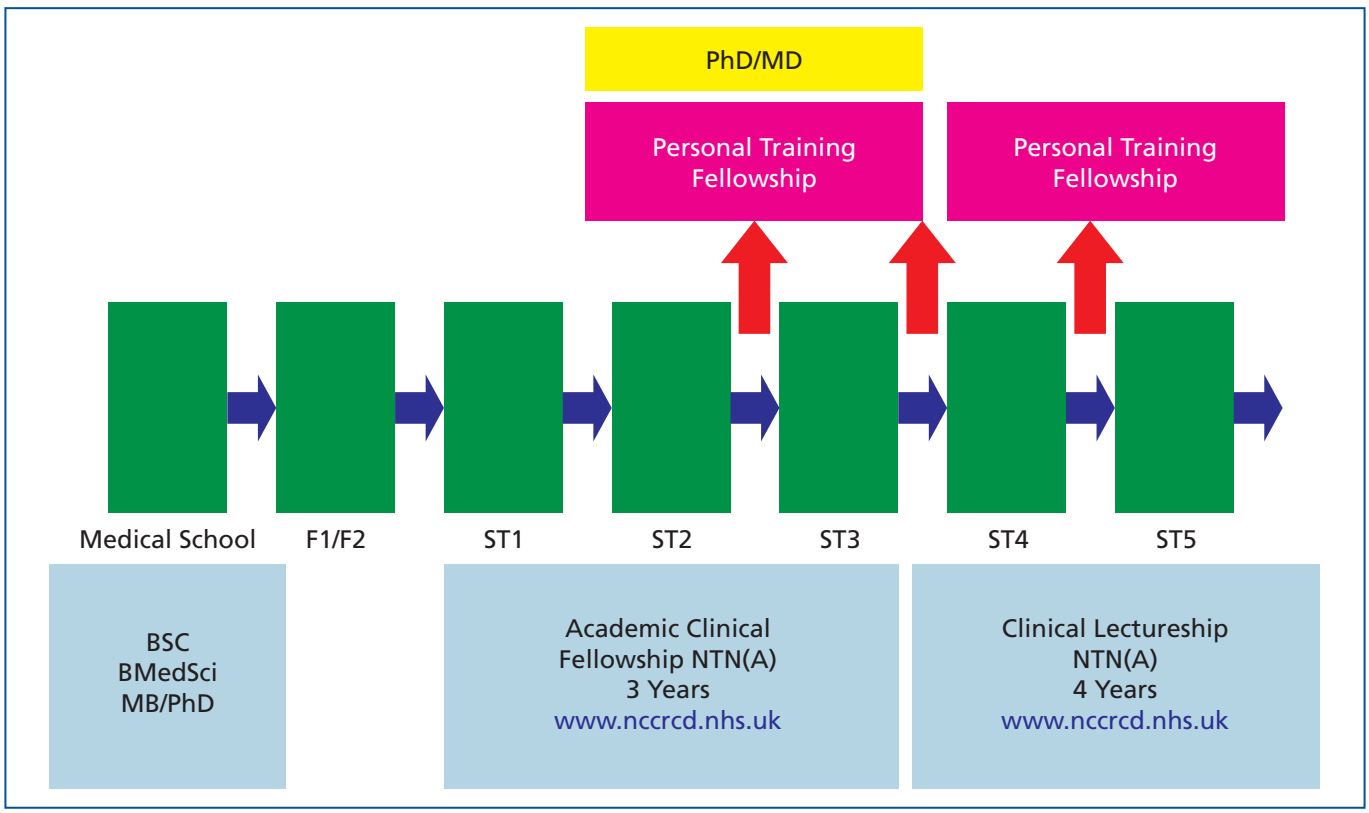
Research funding applications are notoriously complex, arduous and highly competitive, while work as a research trainee demands long antisocial hours, sometimes working independently on repetitive time-consuming tasks with little or no evidence of progress. However, the benefits of undertaking a dedicated period of study in a chosen field are manifold. Trainees undertaking research gain extensive practical laboratory skills and insights which in turn facilitate their understanding of the application and limitations of clinical and diagnostic investigations. Moreover, increased awareness of research and statistical methods improves a trainee's critical appraisal skills and ability to understand and interpret scientific and clinical research papers. Similarly the opportunity to plan and organise a research project nurtures time and financial management skills. Indeed, all skills acquired through research are transferable to clinical practice and undoubtedly enhance an individuals' overall training experience.

For those wishing to pursue a longer-term future in research, gaining a higher degree as part of Haematology or Transfusion Medicine training serves as a passport to entry into a career in academic medicine. However, the United Kingdom has, until recently, lacked a clear pathway for trainees wishing to pursue an academic career. Indeed, the lack of academic career structure is not unique to Haematology but affects academic medicine as a whole.

When to do research?

The obstacles to undertaking research during training and difficulties in career development in academic medicine were identified by the Walport report which highlighted the lack of a clear entry route into research and subsequent transparent career pathway, the inflexibility of the current training programme and absence of structured and supported posts on completion of training. In response to these failings, the report advocated the establishment of an integrated clinical academic training pathway and the creation of dedicated academic training posts (Figure 1); the posts are managed by the National Institute for Health Research (NIHR) Coordinating Centre for Research Capacity Development (NCCRCD). The recommendations were largely supported and upheld by the subsequent Tooke report.

Figure 1: The integrated clinical academic training pathway



Opportunities for research begin at an undergraduate level in medical school with an intercalated degree. The new integrated clinical training pathway offers trainees with an interest in research the opportunity to apply competitively for an Academic Training Fellowship, usually of three years duration, during the early years of specialty training (ST). This provides a clinical and academic environment in which 25% of the trainee's time is dedicated to research, to allow trainees to prepare an application to compete for funding for a personal training fellowship working towards a period of research and higher degree. 25% of the trainee's time is dedicated to research, allowing preparation of a research proposal and submission of an application for a personal training fellowship. Successful candidates would undertake the research project and return to specialty training, usually at ST4 level, following completion of a higher degree. Post-doctoral research may then be pursued by further competitive application for a Clinical Lectureship, usually of four years duration, during which time award of Certificate of Completion of Training (CCT) would be expected, with subsequent progress to senior research posts.

It is apparent that the integrated clinical academic training pathway aims to address the deficiencies identified by the Tooke report, providing a clear structured route into research for trainees, increased flexibility and creating posts on completion of training. However, a potential failing of the new pathway may lie at its very heart. Trainees following the conventional clinical training pathway may also choose to undertake research during their training and can also apply for funding of research projects and higher degrees. Indeed, the very structure of the integrated clinical academic training pathway may create a two-tier training system, disadvantaging trainees who follow the conventional clinical training pathway and find themselves competing with Academic Clinical Fellows for personal research training fellowships; the latter having had dedicated time to prepare such research proposals and funding applications.

Regardless of the career pathway followed by an individual trainee it is vital that those wishing to undertake research plan ahead as organising a research proposal takes a very long time; preparation and submission of an application, short-listing and interview can take in excess of 12-18 months, if successful at all. Post-graduate deaneries impose restrictions on Out of Programme Experience (OOPE) applications during the final year of training and many will decline such requests. Moreover, it is important to consider the timing of MRCPath examinations and the time required to write-up and submit a higher degree thesis and papers, particularly following return to clinical training.

Where to do research?

For many trainees the question of where to undertake research will be answered by social commitments and constraints, for others there may be the opportunity for mobility. In such cases, it is equally important to consider the research record of the department or laboratory and the experience of the supervisor in supporting and guiding clinical trainees within the laboratory. Local, national and international meetings provide an ideal opportunity to meet and talk to prospective supervisors about research projects and funding opportunities.

Research opportunities may be found through advertised established posts, providing a research project, salary, funding and potential to work towards a higher degree. Such posts are often associated with a clinical commitment and are frequently advertised in medical journals or on-line (Table 1). Alternatively, trainees may wish to discuss a specific research idea with a chosen supervisor and subsequently apply for a personal research training fellowship to obtain funding. Many organisations and charities provide funding in the form of training fellowships for trainees wishing to pursue research in a field related to Haematology or Transfusion Medicine (Figure 1). Personal training fellowships, awarded to a named individual, are intensely competitive and require the submission of a structured scientific research proposal, evidence of knowledge of current literature, a concise research plan and detailed costings; preparation of such applications should be undertaken with the assistance and support of an experienced supervisor.

How to do research?

Prior to starting research it's essential to identify a sponsor, to ensure compensation arrangements are in place for negligent and non-negligent harm and obtain approval from Research Ethics Committees (REC) and NHS Research and Development (R&D) committees. The on-line Integrated Research Application System (IRAS) captures information for approval from REC, R&D, the Medicines and Healthcare products Regulatory Agency (MHRA), the Patient Information Advisory Group (PIAG), Administration of Radioactive Substances Advisory Committee (ARSAC) and the Gene Therapy Advisory Committee (GTAC). In some centres, approval may already be in place, whereas in others, it will fall to the individual investigator to complete the required applications (Figure 2). Once the work has started, self motivation and time management are essential due to most research involving a highly variable schedule, dependent on the availability of samples from donors or patients, access to reagents and equipment. During quiet times it's vital to read and build a library, be it in a filing cabinet or using a computerised reference manager. Regular meetings with supervisors enable project methodology to be planned in advance as well as allowing early identification of problems. Keeping a diary, recording experimental details and results, in addition to filing all paperwork, facilitates subsequent preparation and publication of results and ultimately completion of the work.

From a Haematology training perspective it's beneficial to incorporate clinical work into the period of laboratory research. This can be achieved by supernumerary attendance at clinics or participation in on-call rotas, providing care is taken not to become overwhelmed by clinical commitments.

Table 1: Examples of sources of information regarding advertised research posts and funding opportunities for personal research training fellowships in Haematology-related disciplines

Sources of information for advertised research posts
www.careers.bmj.com
www.clinicalacademicjobs.org.uk
www.nature.com/naturejobs/index.html
www.newscientistjobs.com/jobs/default.aspx
Funding and personal training fellowships
Biotechnology and Biological Sciences Research Council www.bbsrc.ac.uk
National Institutes of Health www.nih.gov
Medical Research Council www.mrc.ac.uk
Wellcome Trust www.wellcome.ac.uk
Cancer Research UK www.cancerresearchuk.org
Association of Medical Research Charities www.amrc.org.uk
Leukaemia Research Fund www.lrf.org.uk
Kay Kendall Leukaemia Fund www.kklf.org
British Heart Foundation www.bhf.org.uk
BSBMT www.bsbmt.org

How I do research

From a personal point of view, the opportunity to undertake three years of research in immunology, working towards a PhD, funded by a Wellcome Trust Clinical Research Training Fellowship, has added greatly to my Haematology training. I have gained experience in laboratory techniques and acquired an understanding of their limitations, learnt new skills in computing and management from attendance at a taught research training programme, had the opportunity to teach and acquired transferable skills which will be applicable to clinical care.

While the prospect of undertaking a three year higher research degree may appear daunting and the concept of a compulsory research element in Haematology training likely to prove untenable, the benefits gained from doing research are far-reaching. Incorporating of an optional period of research into all Haematology and Transfusion Medicine training programmes should be considered. Indeed, many programmes already include a research post, allowing trainees to experience laboratory research and enabling those who wish to pursue further study and work towards a higher degree, to prepare a definitive research proposal. Extending this to all training programmes can only be beneficial from an individual trainee's perspective and to the future of Haematology and Transfusion Medicine research in the United Kingdom.

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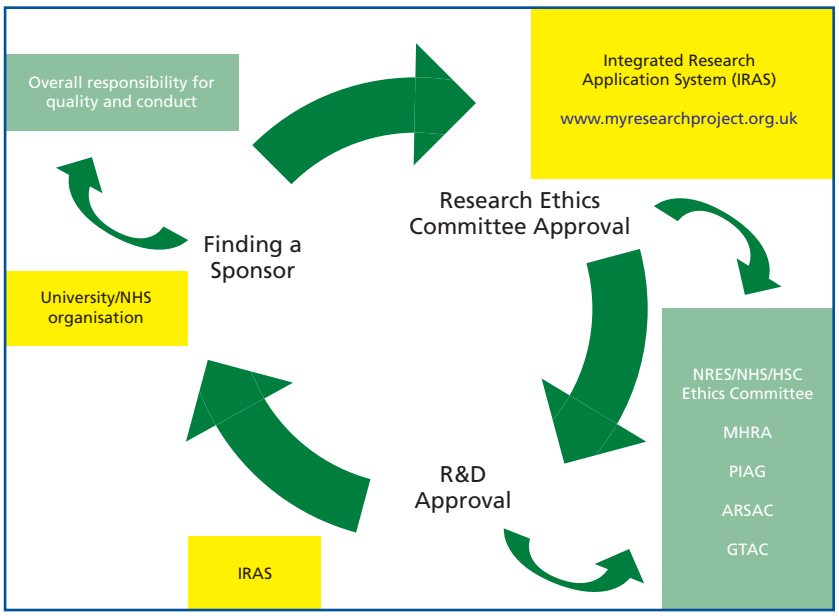


Figure 2: Regulatory approval processes prior to starting research

How I do research: The Professor's Perspective

The specific methods and means of conducting research are the staple of undergraduate and technical courses. Less time is devoted to the more general principles of how scientists actually do research. As we learn and begin to do experimental work we unconsciously absorb the attitudes and approach of senior colleagues, but it is much harder to pin down exactly what we are being taught. Several very distinguished authors have tackled this problem and here I have distilled some of their thoughts and reflections.

When I first started doing experimental work I wondered if any of the work would ever produce new observations let alone anything of help to medicine or science. It is very easy to become discouraged when starting out and it takes time to develop confidence that experimental or clinical scientific work will reap rewards. Here, it does help to have some historical perspective.

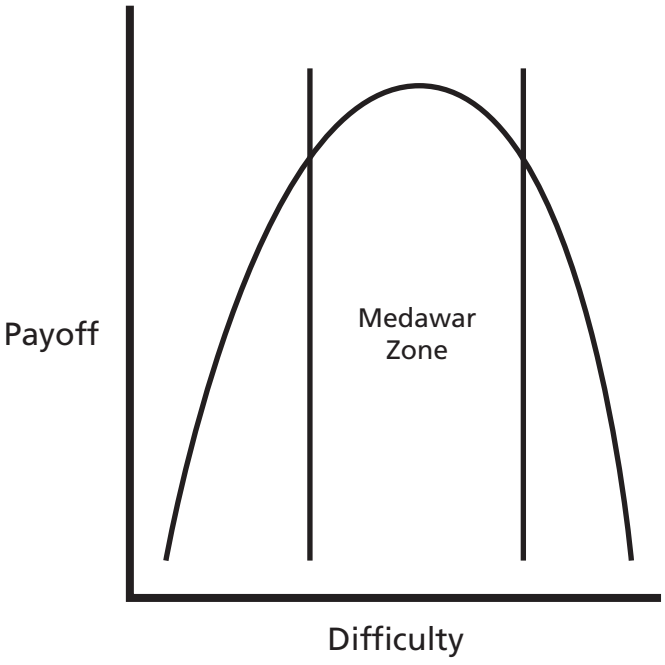
Francis Wheen has captured the importance and relevance of our systematic approach to understanding the world and in his very entertaining book *'How Mumbo Jumbo Conquered the World'*. He reminds us how the scientific revolution in Europe began with the Enlightenment, which fostered the attitude that certain truths about the world could be found through deduction or observation and so transform the quality of life. This has indeed been tremendously successful. We only have to look back in Transfusion Medicine and see the sepia pictures of arm-to-arm transfusions from the 1930's and realise how much has been achieved within living memory. Although our own efforts seem very small, science always builds on what has gone before and so the growth of knowledge is exponential and success spectacular after only a few decades.

Moreover, the French biologist Francois Jacob has emphasised that science is not the work of few great scientists but is essentially a cooperative project. Scientific ideas can only be pursued when a series of preconditions have been made and then several people may then make the same discovery simultaneously, most famously the Theory of Natural Selection was proposed at the same time by Darwin and Wallace. A young scientist starting out must have the confidence that they are joining a collective enterprise that has not just the potential to help others but an unrivalled track record in doing so.

The philosopher Immanuel Kant encouraged thinkers and scientist to have the resolve and courage to understand the world and exhorted us to, 'Dare to know!' When we examine our own work or organisation we can soon see areas or activities that could be improved by having such confidence and resolve to understand why things aren't working as well as they could. There are plenty of problems still left to solve!

What are the qualities of a 'good' scientist? Scientists are as varied in personality as any other group, but many would agree that two traits are very common in successful scientists – tenacity and enthusiasm. My own favourite example of tenacity is Ronald Ross who discovered the life cycle of the malaria parasite in mosquitoes in India in 1897 by the laborious two hour dissection of numerous trapped mosquitoes. His description of finding the first parasite is as moving as it is inspiring, "…I must have examined the stomachs of a thousand mosquitoes by this time… I had scarcely commenced the search of this mosquito when I saw an almost perfectly circular outline before me …and another …in each of these was a cluster of small granules as black as jet and exactly like the black pigment granules of *Plasmodium* crescents." Enthusiasm needs no explanation but worth emphasising is the quality most team leaders look for in new students or senior staff. Without enthusiasm for work little is likely to be accomplished.

How then do we choose a scientific project? There is so much that could be done, but what is most likely to be productive? Peter Medawar, a Nobel Prize winner for his studies of tolerance in transplantation, said, "To make important discoveries, ask important questions," and in his famous seemingly contradictory aphorism, "Science is the art of the soluble". How can we reconcile novelty and feasibility? One attempt to show this graphically is the Medawar Zone – where there is an optimal balance



between payoff and difficulty of a problem. In other words, we have to try and tackle important problems just within our capability – that stretch us, but that are doable. Judging this balance is something we are trying to do all the time.

Where do we start our important yet yielding problem? Mark Davis, who cloned the T-cell receptor, has pointed out that following the crowd is frequently fruitless. The leaders will be far advanced and travelling fast. Instead, try and concentrate on what is missing from the picture or what are the 'black holes'. This is really difficult and requires not just understanding and synthesizing the old and new literature, but also having a hunch about the missing pieces.

To make progress in any area you must know the ins and outs of the tools and techniques that are central to your interests. You have to understand why methods don't work if you are to innovate. It is tempting to apply the technique of the month, and waves of unsuccessful fellowship applications have used tetramers, microarrays and/or proteomics to any old problem without thinking – is really appropriate? Sometimes it is necessary to leave the latest methods and to resort to brute force, or the long and arduous approach, and here confidence, tenacity and judgement are needed to optimise the chances of success.

Contrary to popular myth, scientists do not usually work alone. No one can master all the techniques and collaborations are frequent and are seen as a source of strength not weakness by funding bodies. Collaborations do vary from a simple exchange of reagents to the valuable but occasional wholesale sharing of ideas and results. Is always helpful to try and improve collaborations but some just don't work. As in life, acquaintances are many but friends are few!

In all research but especially in clinical science, all the ideas in the world aren't any use without the right resources. Well-defined clinical cohorts and samples, panels of reagents or cell lines take foresight, time and care to assemble but are vital to testing hypothesises. We were recently able to collaborate with colleagues in Kenya who had collected samples from children with cerebral malaria over ten years to show that high levels of erythropoietin protect children with malaria from neurological damage or death (Casals C, PNAS, 2008).

So having started our studies what do we look out for from day-to-day? We often say, the experiments 'haven't worked'. Sometimes, there is a trivial error but more often that we may think the experiment may well have 'worked' but has simply not given the answer we expected. Failure is educational as our experiments are the way we find out about our subject and should wherever possible be a way of gaining insight. Making progress often throws up new and unexpected data. Group leaders have to remember that most advances are made by post-docs and students proving their supervisors wrong. On a grander scale, if you are breaking new ground, expect opposition to any really important question if it falls outside of conventional wisdom. However, sometimes things really don't work out that well. It happens to everyone, even the best and Medawar recounted to my real surprise, "Twice in my life I have spent two weary and profitless years seeking evidence to support some dearly loved hypothesis that later proved to be groundless…times such as these are hard for scientists". Hopefully, such unsuccessful work does not occur at critical time in one's career!

But looking in the bright side, let's assume all has gone well and a paper is to be written, remembering papers are not just technical reports but stories with a beginning, middle and an end. It is always stimulating to aim for the best journals. This is easier said than done but one way to really produce high calibre work is to imagine from the outset that you will be writing a paper that people in the field must read not just might read. Writing papers is necessary to get more funding but is not enough on its own. Many clinicians and scientists begin research but few continue with post-doctoral experience and well structured funding schemes are required to develop good independent scientists. Here institutional support for scientific approach and scientific work is crucial and we have been fortunate that both NHSBT and our professional colleges have had and continue to have such 'enlightened' attitudes to research.

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UK NEQAS for Blood Transfusion Laboratory Practice - Evolution or Revolution?

UK National External Quality Assessment Service (NEQAS) is celebrating 40 years of quality (Figure 1). The Haematology and Chemistry Schemes were launched in 1969, paving the way for the rest of pathology.

Figure 1:

40 YEARS OF QUALITY
1969 UK NEQAS 2009

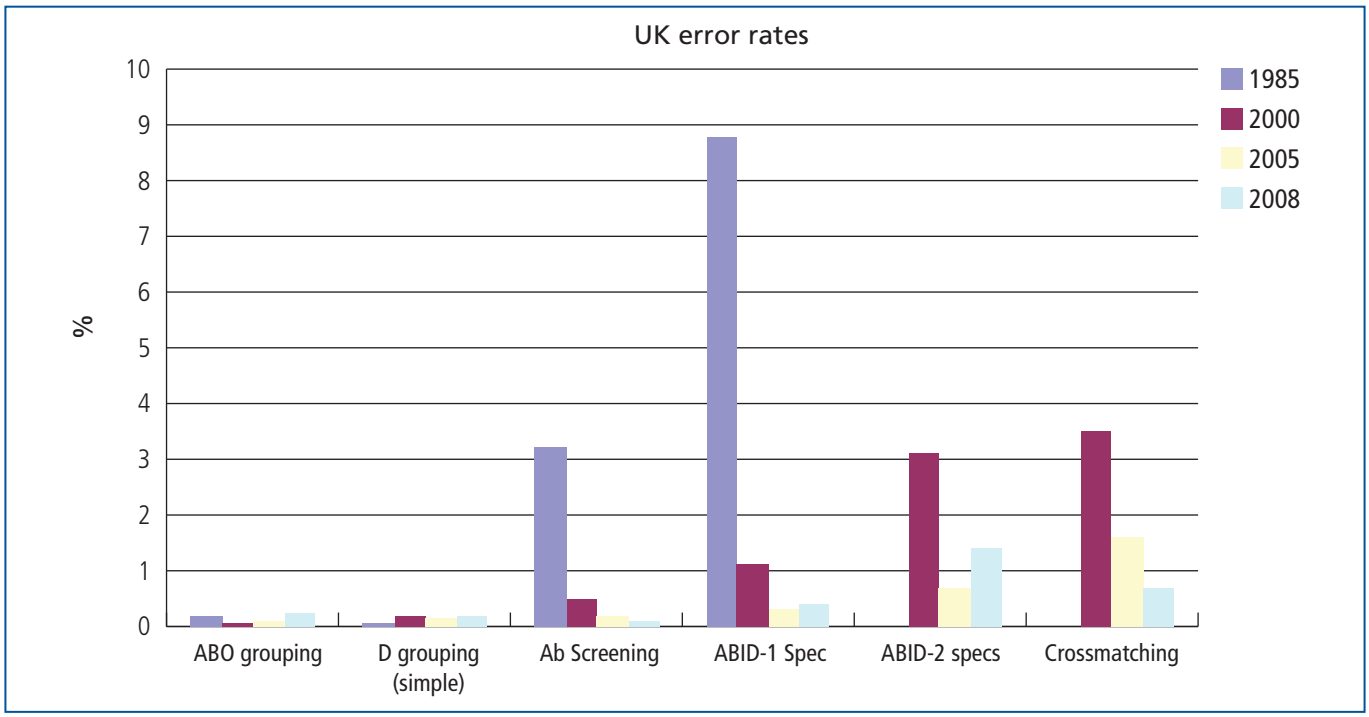
The Blood Transfusion Scheme is an essential tool for assessing the proficiency of participating laboratories in blood grouping, and detection and identification of red cell antibodies which might cause transfusion reactions. It is 30 years old this year. National Quality Control for Blood Group Serology was born in 1979 when the first pilot exercises for crossmatching were distributed, under the direction of Dr Sandy Holburn at the Blood Group Reference Laboratory in London. This happened to be the year I started work at King's College Hospital, and I'm sure I remember participating in that first pilot (little did I realise where my future would lie…). By 1982 these NEQAS exercises had become a routine, if sometimes dreaded, part of the laboratory's practice, with the introduction of ABO/D grouping and red cell antibody screening assessment in 1981 and 1982 respectively, followed by antibody identification in 1984.

In the early days, overall performance was a real concern, with 30% of laboratories unable to detect anti-D at 0.3iu using an enzyme technique. Antibody identification results were even worse, with only 8% of laboratories correctly identifying a mixture of anti-D+Jk^a in one auspicious exercise. Revolutionary improvements in the quality of reagents, including the introduction of monoclonal antibodies, were mirrored by significant improvements in EQA performance. In addition, the first decade of UK NEQAS exercises provided masses of evidence demonstrating areas of poor practice, e.g. pooled screening cells, one stage enzyme techniques and plastic tubes for the indirect antiglobulin test (IAT).

Column agglutination and solid phase technologies brought major change to practice in the 1990s, and there were some controversies surrounding their relative sensitivity. Differences in detection rate of a range of antibodies in UK NEQAS exercises demonstrated that no single technology was the best at detecting all antibodies. Undoubtedly, one of the main benefits of these new technologies was the opportunity they provided for the introduction of automation, into what had previously been entirely manual systems.

Performance in all aspects of blood group serology continued to improve, with error rates in antibody screening becoming vanishingly small (Figure 2). However, in the past 12 years, SHOT haemovigilance data

Figure 2:



has shown that laboratory errors are still occurring, and continue to be the primary factor in causation of a third of all cases of incorrect blood component transfused (IBCT). The majority of these are due to procedural rather than testing errors, and a similar pattern is seen in EQA exercises. As a consequence, the emphasis of the exercises has shifted towards assessing different aspects of serological testing and interpretation, and wider laboratory procedures. The Scheme changed name from Blood Group Serology to Blood Transfusion Laboratory Practice in 1999 to reflect this.

Although weak antibodies are still distributed to assess detection rates in screening and crossmatching, more complex ABO/D typing exercises are included on a regular basis: direct antiglobulin test (DAT) positive samples to assess the level of false positive typing of D negative samples, and mixed field reactions for both ABO and D typing, are two examples. Emergency testing scenarios are also included, which give a useful insight into laboratory practice where blood is required urgently – SHOT data shows that a disproportionate number of errors occur outside of core hours, so this is clearly an important area for monitoring. These exercises demonstrate the level of compliance with current British Committee for Standards in Haematology guidelines, and provide the data and impetus to inform guideline review, by identifying potentially dangerous practice.

UK NEQAS is in a good position to identify and share some of the causes of error, because we are able to talk to transfusion laboratory staff when errors have occurred, and are often able to report the causes for the benefit of all participants. Over the past decade, there have been many examples including:

- ABO grouping errors occurring where lone workers have undertaken manual testing;
- D typing errors where staff have not fully understood the nature of the kits and techniques in use, and have based their interpretations on weak positive reactions or have overlooked positive controls;
- Antibody screening errors, where automation has apparently missed strong positive antibodies, probably due to sampling of air bubbles rather than plasma;
- Antibody identification errors, where neither the process of antibody identification nor the clinical significance of red cell antibodies has been understood;
- Red cell phenotyping errors where reagents have been used uncontrolled and by inappropriate techniques.

In addition to these problems, which often relate to gaps in knowledge, training and experience, there is the ever present problem of transcription and transposition error, particularly in manual grouping and crossmatching. Interestingly, there have been no automation failures in antibody screening since exercise 05E6 in 2005, probably reflecting improvements in error detection and liquid level detection of the automation software.

With the exception of errors that relate specifically to completing the UK NEQAS result sheet or web-screen, or being unable to use routine procedures, the nature of all of the errors described are reflected in those reported to SHOT. These types of error are harming patients and when they occur in a EQA exercise, should be seen as a 'free lesson', a learning opportunity, perhaps even as a 'near miss', and investigated as such.

The UK Transfusion Laboratory Collaborative is publishing minimum standards for hospital transfusion laboratories, a series of recommendations focussed on the use of technology and on the education, training and assessment of staff, with the aim of reducing laboratory errors reported to SHOT by 50% by 2011. If these recommendations are implemented, all laboratories make full use of secure automation, and are able to employ appropriate levels of staff with the required level of knowledge and training, we should also see a further reduction in UK NEQAS errors.

With the advent of molecular techniques for blood group genotyping, I don't imagine that there will be a requirement for an EQA scheme for blood group serology in 30 years time, but the scheme will need to evolve to meet the challenge of the molecular revolution, and the wider aspects of laboratory practice will still need to be monitored and assessed – thankfully without me!

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Transfusion Support for Liver Transplantation

Blood transfusion in liver transplantation

Approximately 650 liver transplants are performed each year across the UK. Liver transplants are either urgent, for acute liver failure or elective, indicated by end stage liver failure caused by cirrhotic, cholestatic, metabolic or (exceptionally) malignant diseases.

Liver transplantation is inevitably associated with blood loss. Blood loss ranges from insignificant to massive rapid haemorrhage. Risk factors for haemorrhage are well described in population terms but still do not allow accurate prediction of bleeding in the individual patient. However, blood use has declined considerably as liver transplantation has reached maturity. Twenty years ago, mean intraoperative packed red cell requirement was 20 units, compared with a current median use of five units per case. There are several explanations for this, which will be outlined in this article.

Factors contributing to blood loss

Portal hypertension

Only 20% of hepatic blood flow derives from the hepatic artery. The portal vein accounts for 80%. Structural changes associated with cirrhotic liver disease result in increased portal pressure (sometimes to values approaching arterial pressure). The process is progressive, with development of varices as a result of distension of the mesenteric venous system and development of venous collateral flow. In addition to raised venous hydrostatic pressure, blood pooling results in an increased volume in the splanchnic circulation, further exacerbating the risk of bleeding during surgery. These effects may be mitigated by partial decompression of the portal/mesenteric venous systems by formation of spontaneous portasystemic shunts (e.g. splenorenal) and flow through other venous collaterals (abdominal wall etc.).

Coagulopathy

Synthesis of clotting factors becomes critically reduced and results in a prolongation of prothrombin time when the functional hepatocyte mass is reduced to around 15%. This may be exacerbated by cholestatic jaundice, resulting in reduced absorption of fat-soluble vitamins and hence deficiency of vitamin K dependent clotting factors and protein C. There is also reduced production of the antifibrinolytic factors (antithrombin, alpha 2 antiplasmin etc) and increased circulating mediators of fibrinolysis, resulting in a complex picture. Interestingly, the severity of coagulopathy does not feature as a major outcome predictor in multivariate analysis, presumably because it is relatively amenable to treatment.

Platelet dysfunction

Platelet numbers and function may both be reduced owing to a combination of hypersplenism, reduced thrombopoeitin production and abnormal renal function. Platelet count is an unreliable indicator of bleeding risk and functional testing, including thromboelastography and the newer platelet function analyser technologies, will become increasingly helpful for assessing status.

Surgical technique

Surgery is divided into three phases: dissection, anhepatic and reperfusion. During dissection, structures surrounding the liver are mobilised and blood vessels ligated. There is significant potential for haemorrhage at this stage, particularly where retrocaval structures need to be dissected. This risk is exacerbated by varices and adhesions, hence surgical technique must be meticulous.

During the anhepatic phase the vena cava is clamped and the portal vein, hepatic artery and bile duct divided, allowing the liver to be removed with a portion of the vena cava. The donor liver is then inserted, bile duct and vessels anastomosed prior to the final phase of reperfusion. Throughout the anhepatic phase coagulopathy worsens and a tendency to fibrinolysis develops. The citrate load from blood products cannot be metabolised. The patient cools and becomes acidotic, both of which further impair coagulation.

Why is it necessary to minimise blood transfusion?

Cross matching liver disease patients can be challenging as they are rarely transfusion naive, with approximately 6% having clinically significant preformed alloantibodies. Large transfusions are associated with a higher mortality post liver transplant. Retrospective studies have demonstrated declining survival with increasing transfused volume of red cells (RBCs) and fresh frozen plasma (FFP). In addition, when platelets have been transfused with RBCs there is a negative association with survival.

It is desirable to minimise blood product use both to avoid transfusion-related complications and to conserve blood stocks.

Factors reducing blood component requirements

Reducing portal venous pressure

Portal venous pressures can be reduced pharmacologically (for example with propranolol or terlipressin) or mechanically. Preoperatively this may be achieved by portosystemic shunting. Intra-operative strategies include creation of a temporary portocaval shunt to decompress the portal system passively, or active decompression using pumped venovenous bypass (lower inferior vena cava and portal vein to superior vena cava).

Correction of coagulopathy and use of antifibrinolytics

Abnormal coagulation is corrected by a number of ways including preoperative vitamin K and prothrombin complex concentrates (PCCs). The availability of fibrinogen concentrate may prove useful as a more standardised alternative to cryoprecipitate to correct severe hypofibrinogenaemia. FFP is used sparingly as it is associated with adverse reactions including acute lung injury, which has a higher reported incidence in liver transplant recipients. Similar problems have been reported with plasma-rich platelet transfusions in this setting.

Intraoperatively, to aid clot stability, fibrinolysis may be attenuated by antifibrinolytics such as tranexamic acid, though this must be balanced against the possible risk of prothrombotic complications (pulmonary, hepatic artery).

Restrictive haemoglobin targets

By maintaining a haematocrit between 0.26 – 0.32, blood flow is optimised, yet allowing adequate oxygen delivery. This reduces transfusion needs, and also reduces the risk of the catastrophic complication of post operative hepatic artery thrombosis and graft failure.

Cell salvage

This process aims to re-infuse the patients own red cells, hence reducing blood transfusion requirements. Relative contra-indications include malignancy and infected ascites. Intraoperative cell salvage (ICS) is now routinely used in liver transplant surgery, although in many cases insufficient blood is retrieved to be reinfused. However, in the rare cases of massive blood loss, ICS accounts for about 50% of the transfused red cells.

Near patient testing

Point of care monitoring devices such as thromoelastography (TEG) have had a huge impact with respect to understanding haemostatic mechanisms and guiding the appropriate use of blood components. These devices provide valuable information regarding coagulation, clot formation, clot strength, platelet function and fibrinolysis.

Maintaining homeostasis

During the pre, intra and post operative course it is crucial to maintain normothermia and metabolic "stability". Hypothermia and acidosis exacerbate coagulopathy and contribute to organ dysfunction. Rapid infusion devices (eg. Level one infuser) provide effective fluid resuscitation, with the added advantage of efficient fluid warming.

Summary

Blood transfusion requirement for liver transplantation has declined dramatically in recent years owing to advances in surgical and anaesthetic techniques, improved understanding of complex haemostatic disorders, lower transfusion triggers and devices such as TEG and cell salvage. Continuing advances may lead to blood transfusion becoming the exception during liver transplantation.

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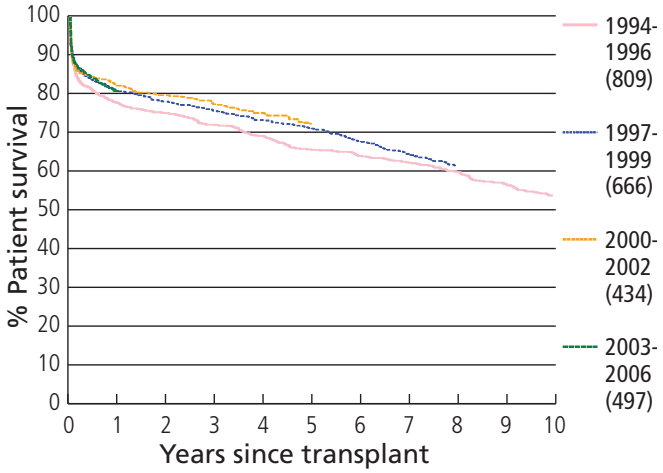
Heart Transplantation

Long term survival following cardiac transplantation (figure 1) continues to improve in the United Kingdom and is similar to that reported to the registry of the International Society for Heart and Lung Transplantation. In the current era five and ten year survival rates around 75% and 60% respectively are to be expected.

Figure 1: Survival following adult cardiac transplantation in the UK (NHSBT data).



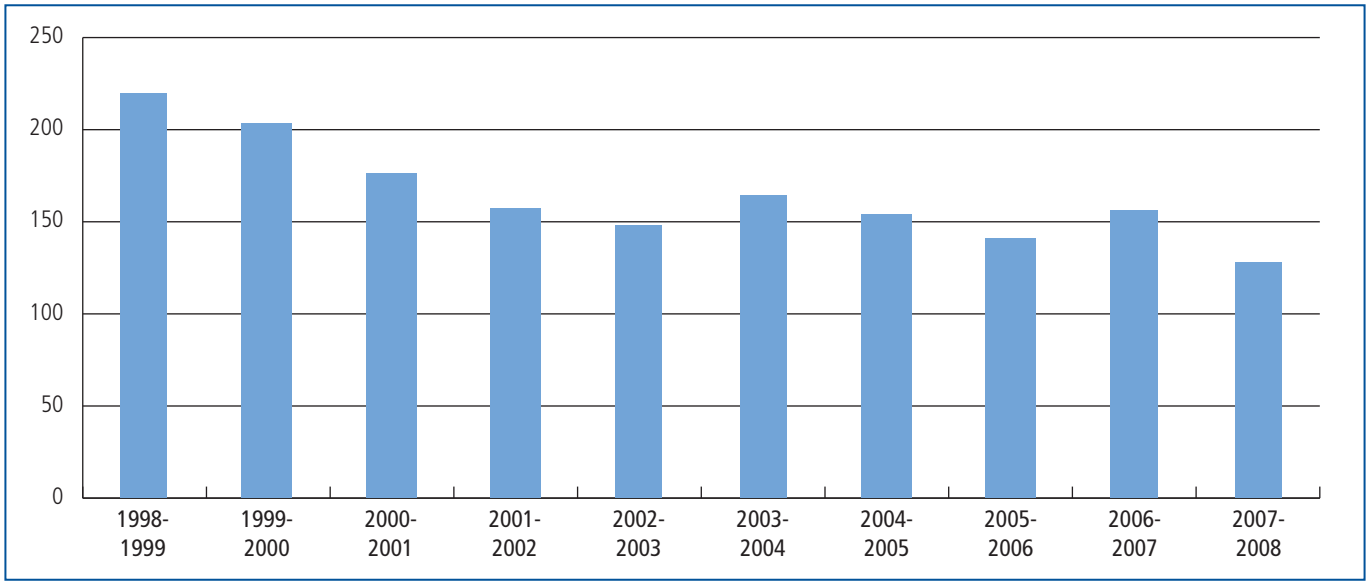
In the history of cardiac transplantation, the introduction of ciclosporin in the 1980s stands out as a major turning point in improving survival. Since then, the use of statins early after transplantation has not only led to a further decrease in clinically severe rejection episodes and improvement in survival, but also to a reduction in graft coronary artery disease. Nevertheless, whilst the incidence of and mortality from acute rejection and graft coronary artery disease (chronic rejection) have declined, the development of graft coronary artery disease continues to be a major cause of morbidity and mortality in the long term. Proliferation signal inhibitors (PSI) such as sirolimus and everolimus show promise in reducing the development of this complication as well as further reducing acute rejection. As these patients are now living longer, with the increased duration of immunosuppression comes the increased risk of developing malignancy which is now almost as likely as coronary artery disease to limit long term survival; however, PSI based immunosuppression is associated with a lower risk of malignancy than calcineurin inhibitor-based regimens. Unfortunately, PSIs have significant adverse effects that limit their widespread use and the combination of multiple agents at lower dose may yet prove to be the way forward.

Despite extending the donor acceptance criteria for potential heart donors in an effort to increase transplant rates, the number of heart transplants in the UK continues to decline (figure 2). It is hoped that the initiative to increase donor numbers in the UK by 50% over the next five years will reverse this trend. In addition, donor optimisation by haemodynamic management has been shown to have potential in increasing the number of donors suitable for heart transplantation.

Tissue typing

With the adoption of flow cytometry for tissue typing in potential cardiac transplant recipients, increasing numbers of patients are found to have pre-formed HLA antibodies. This has resulted in much more work for tissue typing laboratories, with repeat tests, virtual crossmatching and prospective crossmatching of recipients and donors. Whilst the detection of HLA antibodies by flow cytometry is more sensitive than the traditional method of complement-dependent cytotoxicity (CDC) and may be superior in predicting the likelihood of antibody mediated rejection, it does not appear to distinguish the likelihood of short term (three year) survival in kidney transplants.

Figure 2: UK heart transplants 1998-2008 (NHSBT data)



Because of this increased sensitivity, some patients have been deemed to have a much reduced chance of finding a donor according to flow cytometry results; this has led to attempts at eliminating these antibodies pretransplant: plasmapheresis or immunoadsorption, rituximab, immunoglobulin, and immunosuppression with cyclophosphamide and/or mycophenolate are being utilized in various combinations in an attempt to enable patients with end stage heart failure and significant levels of HLA antibodies to find a suitable donor heart. Whether such 'desensitisation' is successful in the long term in eliminating the possible pathogenic effects of these antibodies remains to be seen.

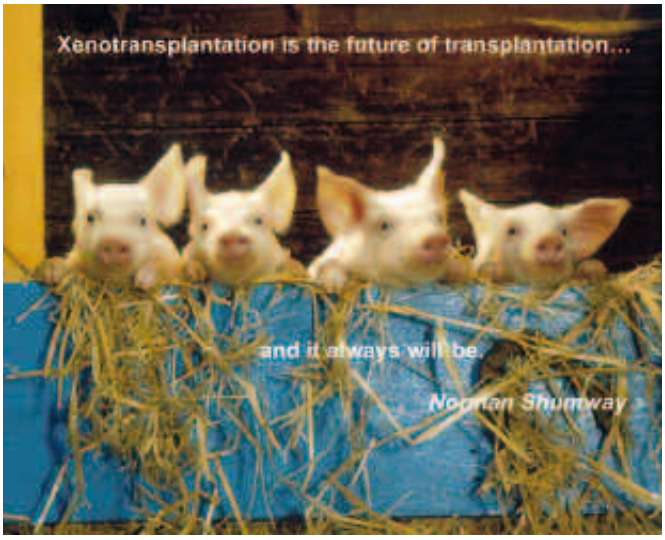
Ventricular assist devices

Ventricular assist devices are seen by many as the long-term remedy for the treatment of end stage heart failure. When only the left ventricle requires assistance (LVAD), then results are significantly better than medical therapy alone, although not yet as good as a transplant. When both ventricles need support (BiVAD) the risks are greater and success lower (figure 3). Nevertheless, both LVADs and BiVADs are utilised as a bridge to transplant in suitable patients; survival post transplant in these patients is comparable to that in patients who have not required VAD support.

The development of HLA antibodies in these patients de novo *after* VAD implantation further complicates the picture, and the relevance of these 'new' antibodies is unclear.

Xenotransplantation

The media excitement in the late 1990s that xenotransplantation, and even human organ cloning, was imminent, and would occur in the present decade,



was somewhat premature. Research continues in an effort to overcome the problems with rejection and potential cross-infection and there is a recent useful commentary discussing the continuing dilemmas that need addressing before clinical xenotransplant trials can begin.

The words of the late, great, cardiac transplant pioneer from Stanford, California, Norman Shumway, who performed the first successful heart transplant in the United States on January 6, 1968, may yet prove to be prophetic: in 2002 he said

"Xenotransplantation is the future of transplantation… and it always will be."

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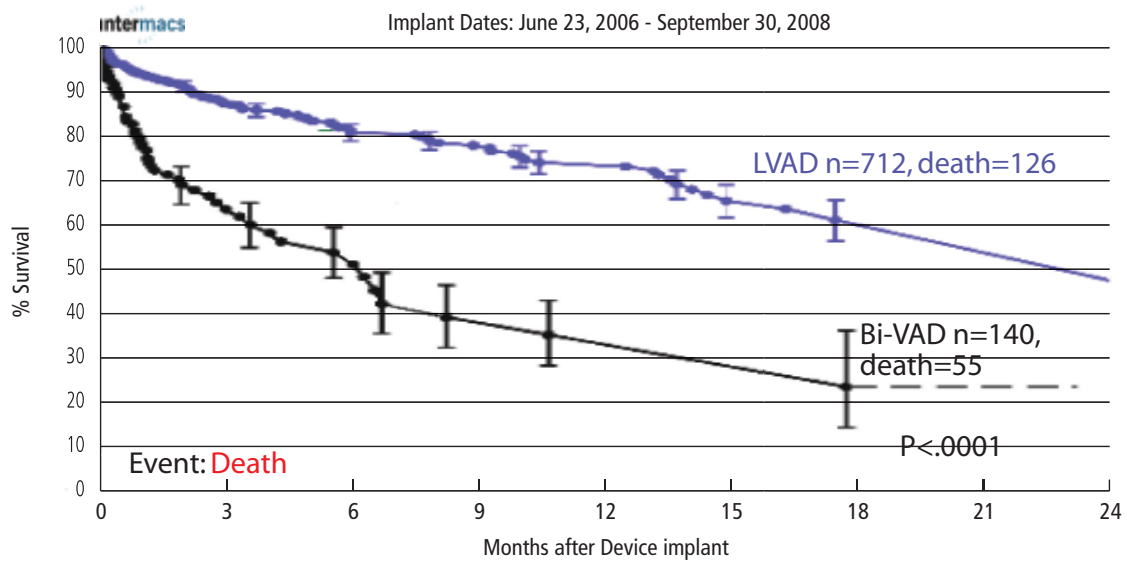
Figure 3: Survival following implantation of ventricular assist device(s)



Tissue Banking Cooperation in Europe

Europe is a very diverse cultural entity. It is represented in a number of different ways. The Council of Europe includes 47 Members States (MS), whereas the European Economic Community, now known as the European Union, which was set up by the Treaty of Rome in 1957, has 27 MS and three Candidate Countries. A number of treaties gave the European Union the competence to legislate. The EU has 23 official languages.

The European Association of Tissue Banks history is strongly linked to the development of tissue banking. The first tissue bank was set up in 1949 in the Naval Medical Centre in Bethesda, Maryland, US, and European tissue banks followed shortly after. In 1952 a bank was established in Heradec, Kralove, 1955 saw the opening of Yorkshire Regional Tissue Banks in Leeds, UK, the following year a bank opened in Berlin and in 1962 one opened in Warsaw. Since that time, many national and regional tissue banks have emerged. The European Association of Tissue Banks was established in 1991 and in 1998 had representative members from 45 countries world-wide, of which at least 19 were outside the European Union. Congresses have been held every year since 1991 throughout Europe. There have been various projects between the European Association of Tissue Banks and national European Associations and often the annual congress is held in collaboration with a national association. There is also cooperation with the American Association of Tissue Banks, which was established in 1976. In 2008, the European Association of Tissue Banks offered 'Sister Association' membership to national tissue banking associations.

In 2004, at the 4th World Congress for Tissue Banking in Brazil, the idea of a World Union of Cell and Tissue Banking was introduced and a second meeting of the World Union of Cell and Tissue Banking was held in 2008 at the 5th World Congress in Malaysia. The attendees included representatives from the Associations of Latin America, Australasian, Asia-Pacific, European and American Association, as well as the World Health Organisation (WHO). It was agreed that the World Union would work towards harmonising local practices, exchanging information, coordinating activities of local member associations and other collaborative working arrangements, which it is anticipated will develop over time.

There are significant tissue banking activities in other organisations and various national blood services within Europe. Recently the European Blood Alliance surveyed its members and determined that there are significant numbers of tissue banks within these blood centres. The WHO has produced important papers on ethical issues relating to access and safety of organ transplantation, human organ and tissue transplantation, and a proposition for a global agenda on transplantation. The International Atomic Energy Agency (IAEA) also has had a role in tissue banking using radiation technology to increase safety of grafts. IAEA has provided training for tissue banking staff and has helped develop standards and regulatory guides.

The history of standards through professional association standards, such as that of the European Association of Tissue Banks and the American Association of Tissue Banks, as well as national guidelines, gave the prelude to the development of the Council of Europe Guidelines for Organs, Tissues and Cells and ultimately contributed towards the development of the European Commission (EC) Directives for Tissues and Cells. The EU Directorate with responsibility in this area (SANCO) commissioned the workshop which was organised by the European Committee for Normalisation (CEN) to develop a European Coding System, a requirement of the European Directives. This is in recognition of the challenges of cross-border tissue distribution and the need for unique traceability of tissues and cells, especially in the context where there may be tens or hundreds of recipients from a single donor and that there is considerable international sharing of substances of human origin. The risk of disease transmission is not zero and there is a need for adverse events and reactions to be reported through an international system of surveillance and vigilance.

The EC also gave initial funding to the EUROCET. This is a European Registry for Organs, Tissues and Cell donation and transplantation, and is available on-line for any European Citizen, whether they be patients, professionals or institutions. This of course requires harmonisation of terminology and will help effective implementation of the EC Directive 2004/23. EUROCET has provided the first registry of authorised or licensed tissue establishments in MS.

The EU Directorate SANCO also funded EUSTITE project, which has developed the requirements for inspections for tissue facilities and details how and by whom inspections should be undertaken and the training they should receive. EUSTITE had links to the Food and Drugs Administration in the US, the American Association of Tissue Banks and the WHO. It has a consortium of ten public sector organisations from ten EU MS, and the WHO. Its two main arms are in developing consensus and best practice in inspection of tissue establishments and in

Adverse Event and Reaction reporting in a supra-national vigilance and surveillance model.

The European Quality System for Tissue Banking project was made up of four working groups which considered standards and procedures, a registry of tissues and cells and found that the need for a common nomenclature was required, training models and accreditation models.

The European Centre for Disease Prevention and Control (ECDC), established in 2005, produces weekly and monthly bulletins and is EU funded. It aims to identify, assess and communicate current and emerging threats to human health posed by infectious diseases and works in partnership with National Health Protection Bodies across Europe and with European experts to develop authoritative scientific opinion about infectious risks.

Phare is the main long term funding instrument for new and applicant countries, to help them in preparation for joining the EU; there is also a funding instrument called TAIEX for new MS and applicant countries to obtain support for short term projects, such as courses and expert visits.

There have been two meetings of the Competent Authorities of MS, in 2007 and 2008, which permitted Competent Authorities to share their experiences in implementing the EU Tissues and Cells Directive and European projects of relevance to their work. The last meeting examined the next steps for a Working Group on voluntary and unpaid donation. It also reviewed TAIEX funded training courses on tissues and cells and guidelines for the European Coding System. It discussed publically accessible registers of tissue facilities in MS, the EUROCET project, reporting on Adverse Events and Reactions and the EUSTITE project.

European projects in tissue banking go far wider than regulation. The European Association of Tissue Bank seeks to support activities in the EU and wider Europe and with professionals in other continents, to provide the continuing development of the association, its members, and the profession of tissue banking. There are many European projects in the field and these demonstrate the rapidly expanding nature of tissue banking as a speciality.

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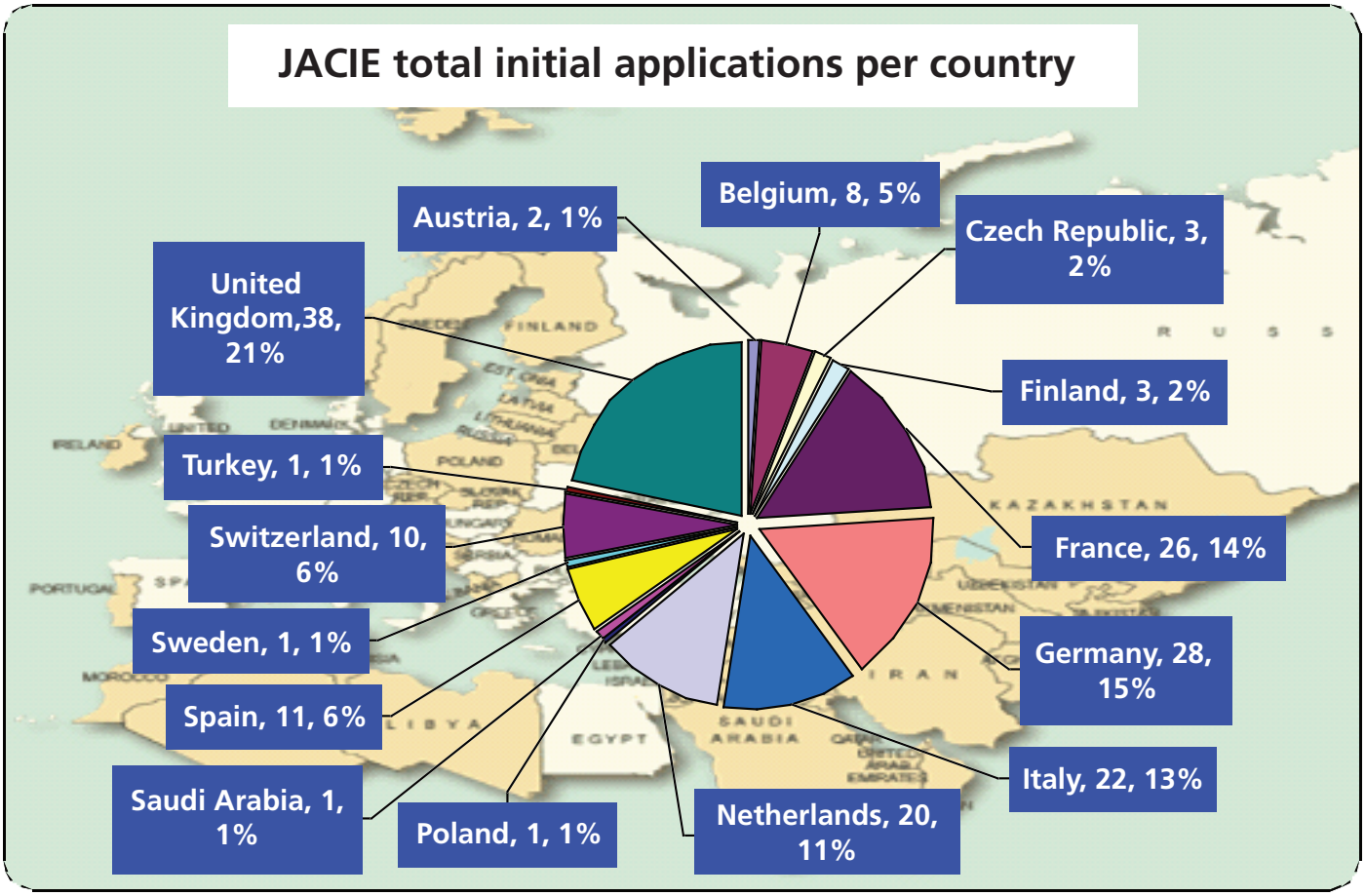
JACIE Accreditation – What is Involved?

Introduction

First of all, what is JACIE? The acronym is a complicated one and stands for the Joint Accreditation Committee of the ISCT – Europe (International Society for Cell Therapy) and the EBMT (European Group for Blood and Marrow Transplantation). It is deliberately similar to the Foundation for Accreditation of Cell Therapy (FACT) which was founded in 1994 in the United States as a voluntary inspection and accreditation scheme for cell therapy programmes. JACIE was founded in 1999 and it initiated an active programme of inspections in Europe in 2004. FACT-JACIE have common standards and accreditation manual which define the requirements of a voluntary system which accredits clinical transplant programmes as well as the cell collection, processing and banking elements that are also covered by current EU legislation. Cell therapy is a rapidly expanding and complex field and in addition to haemopoietic stem cell transplantation (HSCT), stem cell therapies are being applied in the management of patients with solid tumours and degenerative diseases which will affect more than 50% of individuals in Western societies. The development of quality systems is central to compliance with accreditation requirements which have increased considerably in the last decade.

Applying for JACIE Accreditation

The primary aim of JACIE is to improve the quality of HSCT in Europe and elsewhere by providing a means whereby transplant centres, cell therapy product (CTP) collection centres and processing facilities can demonstrate high quality practice. This is achieved through external inspection of facilities to ensure compliance with the FACT-JACIE standards. A further aim is to ensure consistency between the standards and other national and international standards, including the EU Tissues & Cells Directive (Directive 2004/23/EC) and the related implementing Commission Directives 2006/17/EC and 2006/86/EC. Application for JACIE accreditation is through on-line submission of documentation following initial discussions with staff at the JACIE office which is co-located with the EBMT in Barcelona (www.jacie.org). Centres may apply for accreditation as complete programmes comprising a clinical programme, collection



facility and processing laboratory or, for example, as single collection or processing facilities which may serve a number of clinical programmes. NHSBT operates several facilities of this type.

The FACT-JACIE Standards

The standards, now in their 4th edition (2009), describe the requirements for (i) all aspects of clinical HSCT programmes (ii) CTP collection facilities (including both bone marrow and peripheral blood stem cells) and (iii) processing laboratories. The standards also apply to the use of therapeutic cells (TC) derived from the peripheral blood or bone marrow, including donor lymphocytes and mesenchymal stem cells. In addition they apply to the clinical use of Cord Blood stem cells by clinical programmes but not the collection or banking of cord blood, which is inspected and accredited by FACT-Netcord (accreditation body comprised of representatives of both FACT plus the international cord blood organisation Netcord; an article describing their standards for cord blood collection, processing and banking will appear in the next issue of *Blood Matters*).The JACIE website contains a wealth of information that will aid centres that are in preparation for an inspection. At the EBMT meeting in 2008 the JACIE Quality Manual was published for the first time. This is an invaluable guide to implementing quality systems in HSCT programmes in line with the FACT-JACIE Standards.

How to train as a JACIE Inspector

Inspectors are doctors and scientists with expertise in clinical medicine and cell collection or processing laboratory facilities as appropriate that have a minimum of five years experience. All will have attended a JACIE training course, completed a short examination and submitted a CV to the JACIE office in Barcelona from where details of courses can be obtained. Inspectors are expected to be professional, courteous, helpful, and efficient and to respect the confidential relationship between the applicant centre and JACIE.

What does an Inspection involve?

A JACIE inspection lasts one and a half days and involves a thorough review of all aspects of the programme. A detailed checklist submitted on line by the transplant centre beforehand together with the Quality Management (QM) plan and other documents is completed by the inspectors on site and forms the basis for the final report. There is one inspector for each part of the programme (clinical, laboratory and so on) with an additional paediatric inspector for programmes that perform transplants in children. Full details of the process can be found on the JACIE website but, as an example, the clinical inspector will review case notes to verify that data is being correctly recorded and reported, tour the

clinical facility and hold discussions with a wide range of staff including doctors, nurses, pharmacists, data managers and dieticians. At the same time, the collection and processing facility inspectors undertake a detailed review of the facilities, documentation and operation of the apheresis clinic, bone marrow collection facilities (where this is done) and CTP processing laboratories. The inspection team produce a detailed report which is then reviewed by the JACIE Accreditation Committee and the applicant will then be asked to correct any deficiencies that have been found – there are always some! In many cases these are of a minor nature such as corrections required to policy and procedure documents but more major problems have emerged. These have included inadequate inpatient isolation facilities and failure to properly establish and implement a Quality Management (QM) programme. Usually deficiencies are resolved within three to nine months of the inspection and accreditation when awarded is valid for four years, with an interim quality assessment being carried out after two years. The commonest deficiencies found are with QM systems and documentation, donor assessment and labelling of CTP.

Experience of centres implementing JACIE

A recent survey showed that the most difficult part of preparation was implementing the QM system, adverse event (AE) reporting system and other documentation. Lack of a QM culture was cited as by many as an important constraint and the extra resources most frequently required were a quality manager and a data manager. Only 19% of centres needed to improve their physical facilities. It is important for centres to have a designated quality manager who has appropriate experience in QM systems. The level of improvement post-JACIE depended on the level of existing services, so that in some cases failure to demonstrate improvement in e.g. data management might have reflected the fact that good systems were already in use. In some cases, systems for AE reporting were only put in place for accreditation making it difficult to monitor improvements without an established baseline for comparison. Paradoxically, implementing JACIE has caused an apparent increase in AE simply because these were not adequately reported before. All centres surveyed felt that accreditation was worth the effort invested and Healthcare Commissioners increasingly view JACIE accreditation as important. In addition, with the implementation of the EU Directive on Safety of Tissues and Cells (2004/23/EC) it is likely that collection and processing facilities will regard compliance with JACIE standards as important in providing evidence that they are complying with the requirements of the Directive.

The Future

JACIE aims to continue its close working relationship with FACT in the future, setting quality standards for accreditation of CTP collection, processing and transplantation. It is contributing to discussions based on establishing globally-harmonised standards which may, in time, include the clinical use of non-haemopoietic cells.

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Next Edition

NHS Blood and Transplant's activities now include organ donation and transplantation, in addition to blood transfusion and both cell and tissue therapies. This is increasingly reflected in the articles that we publish. To recognise this, Blood Matters is changing its name to 'Blood and Transplant Matters' starting with Issue 29 which is due to be published in December 2009. It will feature articles on:

- Blood Component Transfusion in Apheresis Clinics
- Preventing Transfusion Transmitted Infections
- Antibody Production for Diagnosis and Therapy
- The way NHSBT's Audit and Clinical Statistics works
- Tissue Banking in South America
- The FACT-Netcord Standards
- Transfusion in Malawi

If you would like to comment on any of the articles in this edition of ***Blood Matters*** please email the editor: derwood.pamphilon@nhsbt.nhs.uk

CPD Questions for Blood Matters 28

RECENT CHANGES TO BLOOD DONATION SELECTION GUIDELINES

1) Permanent exclusion as a blood donor

A) Diabetic – treated with Insulin.

B) Hypertension – treated with a Beta-blocker, same dose for 2 months.

C) Diabetic – treated with Metformin, no other problems.

D) Hypertension – treated with ACE inhibitor, same dose for 2 months.

2) New blood donors can be recruited up to

A) 64th Birthday.

B) 65th Birthday.

C) 66th Birthday.

D) 70th Birthday.

3) Regular and returning donors can continue to donate until

A) 65th Birthday.

B) 66th Birthday.

C) 70th Birthday.

D) No absolute upper age.

Audit Of Red Cell Use In Hospitals In The South West And West Midlands

4) What percentage of transfusion episodes occurred in medical rather than surgical cases?

A) 47%

B) 49%

C) 57%

D) 67%

5) Of those transfused with abnormal red cell indices, in what percentage had haematinic investigations been performed?

A) 100%

B) Lesser than 40%

C) 50%

D) 80%

National Comparative Audit Of The Use Of Fresh Frozen Plasma In Adults

6) What percentage of FFP transfusion were given for warfarin reversed?

A) 14%

B) 10%

C) 5%

D) 0%

Haemovigilance: A Safe Investment

7) The following are not new developments in haemovigilance

A) Globalization.

B) Becomes part of a quality system of the Blood Transfusion Chain.

C) Optimal Blood Usage.

D) Report only infective incidents.

Transfusion support for Trauma

8) According to NCEPOD 2007, there are approximately

A) 150

B) 200

C) 240

D) 300

Severe Cases of Trauma Each Week

9) What percentage of casualties require more than 10 units of blood?

A) 1%

B) 2%

C) 5%

D) 10%

10) Military experience has shown that each unit of plasma in a 1:1 ratio with packed red cells was associated with a reduction in mortality from 66% to

A) 50%

B) 23%

C) 19%

D) 15%

UK NEQAS

11) In the 1980s, what percentage of laboratories were unable to detect Anti-D at 0. 3 IU using an enzyme technique?

A) 30%

B) 20%

C) 10%

D) 5%

12) In the first decade of UK NEQAS provided evidence demonstrating which areas of poor practice?

A) Pooled Screening Cells.

B) One stage enzyme techniques.

C) Plastic tube for IAT.

D) All of the above.

13) The following have not had an impact in reduction of red cell transfusion requirements in liver transplantations

A) Assess platelet requirement on rapid platelet counts.

B) Reducing partial venous pressure with terlipressin.

C) Maintaining a haematocrit between 0.26 – 0.32.

D) Point of care testing, such a thromboelestography.

Heart Transplantation

14) Currently five and ten year survival rates around

A) 85% of 70%

B) 75% of 60%

C) 55% of 40%

D) 25% of 10%

Respectively are to be expected

15) Ventricular Assist Devices (VAD)

A) When only the left ventricle requires assistance (LVAD), then the results are as good as a transplant.

B) When both ventricles need support (BiVADS) the risks are lower and success higher.

C) Both VADs and BiVADS are utilised as a bridge to transplant in suitable patients.

D) Survival post transplantation in those supported by a ventricular assist device is poorer than in those who did not require VAD support.

Diary Dates

2009

23-26 August 2009
Fourth Annual Physician Network Symposium.
University of Texas
Boston, USA
http://www.mdanderson.org

24-25 August 2009
1st International Symposium on Critical Bleeding.
Copenhagan, Denmark.
Several internationally renowned experts within the field of anaesthesiology and intensive care, trauma, haematology and transfusion medicine will participate in the symposium and give "state of the art" lectures concerning the management of critically bleeding patients.
For Further Information please visit:
http://www.iscb2009.dk

2-3 September 2009
Advanced Specialist Transfusion Science.
2 day course
Newcastle
http://www.hospital.blood.co.uk

10-12 September 2009
BBTS Annual Conference 2009.
Manchester Central, Manchester
The conference will be held in the centre of Manchester and the social programme promises to make best use of the active night life of this bustling city. For more information:
www.bbts.org.uk/diary/details.cfm?eventId=1543

17 September 2009
Specialist Transfusion Science Theory Modules.
One day course
Leeds
http://www.hospital.blood.co.uk

23-25 September 2009
Transfusion Practice & Transfusion Alternatives.
Reval Latvia Hotel.
Further information please contact: Galina Bukovska Baltic Travel Group tel. +3 716 7228428, galina.bukovska@btgroup.lv
http://www.rigatransfusion.com

28-30 September 2009
IBMS Congress.
ICC, Birmingham
http://www.ibmscongress.com

9 October 2009
TLRs, NLRs and RLRs, pathogens sensors of innate immunity.
BioPark Hertfordshire, United Kingdom
This meeting has CPD accreditation
http://www.regonline.co.uk/TLR09
A full diary of events and training courses can be viewed on the following websites
http://www.transfusionguidelines.org.uk
http://www.blood.co.uk/hospitals
http://www.bbts.org.uk

24-27 October 2009
AABB Annual Meeting. New Orleans, LA.
United States of America.
Contact:
AABB Meeting Services, Tel:+1 301 2156480

14-18 November 2009
XX Regional Congress of the ISBT.
Nagoya, Japan
http://www.isbt-web.org/congresses/default.asp

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