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NHS Blood and Transplant

Blood and Transplant Matters

Information for hospitals served by NHS Blood and Transplant

Inside

EDITORIAL

Welcome to the Summer issue of *Blood and Transplant Matters*. As the non-medical member of the Editorial Board, I find that I often turn to the internet for basic knowledge to help me read and understand some of the articles. For a naturally curious (or maybe just plain nosy) person, I find the breadth of topics discussed fascinating and enlightening, as I'm led into areas I knew little or nothing about.

Two words I do understand though, are risk and safety and reading through this issue's articles I realised how much of what we do is about identifying risks and problems and by reducing or solving them, making things safer and better for patients. NHSBT regards safety as a priority concern, and safety is a theme running through many of the articles in this issue. In the UK and Ireland we regard blood transfusion as a very safe procedure, but we are not complacent and welcome new technologies that are proven to make transfusion even safer. Willie Murphy from the Irish Blood Transfusion Service discusses pathogen reduction technologies and their potential to further increase the safety of blood. Continuing the quest for safe blood, Joanne Mountford discusses progress and the challenges that face us in developing a process for *in vitro* red cell manufacture.

As the government's advisory body on the safety of blood, tissues and organs, SaBTO is responsible for considering a wide range of issues. John Forsythe and Nick Watkins detail some of the issues they have considered and those currently under review. Also, on matters of advice and guidance, the 'Red Book' guidelines, prepared by Joint Professional Advisory Committee (JPAC), have been providing guidance on transfusion practice for twenty years. During that time, there have been many changes in transfusion practice, and new legal standards and requirements. The UK Forum commissioned a review of JPAC, Sheila MacLennan reports the findings.

In Immunology for Dummies, Part 2, Belinda Kumpel takes us through the response mechanisms to transfusion and transplantation, and the strategies employed to overcome the potentially fatal complications these cause. Derwood Pamphilon and Rohini Radia describe the challenges presented by Haemopoietic Stem Cell Transplant patients. They detail how appropriate selection of blood components can help in the management of these patients. Still on the subject of transfusion, following a collaborative project between NHSBT and the SNBTS that looked into the feasibility of nurses prescribing blood, the governance Framework was launched in 2009. Elizabeth Pirie, one of its authors updates us on the progress of this initiative.

Sarah Haynes details how Thromboelastography is a useful tool in determining a patient's blood component requirements and has the potential to improve clinical decision making and ultimately may help to optimise appropriate use of blood components in surgical patients.

IT systems don't always get a good press, but the new online blood ordering system OBOS is one that should. NHSBT worked closely with hospitals and two IT companies to produce a bespoke system that brings benefits to all users. The system is now being rolled out. Heather Aplin reports on a job well done.

Christine Cserti-Gazdewich discusses the difference in how blood group could be a significant factor in how we are affected by malaria. This suggests the possibility of a potentially new strategy as a way of combating this most serious disease. Global warming could soon bring the threat even closer to home, but for those of us fortunate to be travelling to exotic climes now, the article may serve as a reminder to check if antimalarial drugs are recommended.

Since 2006, the HTA has been the watchdog that protects public confidence by licensing organisations that store and use human tissue for purposes such as research, patient treatment, post-mortem examination, teaching, and public exhibitions. It also gives approval for organ and bone marrow donations from living people. Shaun Griffin gives us an overview of their operations now as well as looking into the future.

It's more than 100 years since the first corneal transplant was carried out. Nowadays, around 3,000 take place each year in the UK. Stephen Kaye, Rosalind Stewart and Sharon Mason describe the recent advances in ocular transplants and other treatments vital to restore sight. Corneal transplants rely on the generosity of donors, and as age isn't a factor, most of us could be donors. Please think about it, and – If you believe in organ donation prove it, register now at **www.organdonation.co.uk**

Finally, a celebratory note to end on. "Extraordinary You" is a project to raise the profile of Healthcare Scientists. Helen Gillan reports on the launch event at 11 Downing Street and the book which showcases the breadth of expertise in scientists working in the health service. NHSBT is proud to have six of its scientists recognised in this book. I hope you find this issue as interesting as I do. Please continue to let us have your feedback, news and suggestions for articles.

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Thromboelastography in Clinical Practice

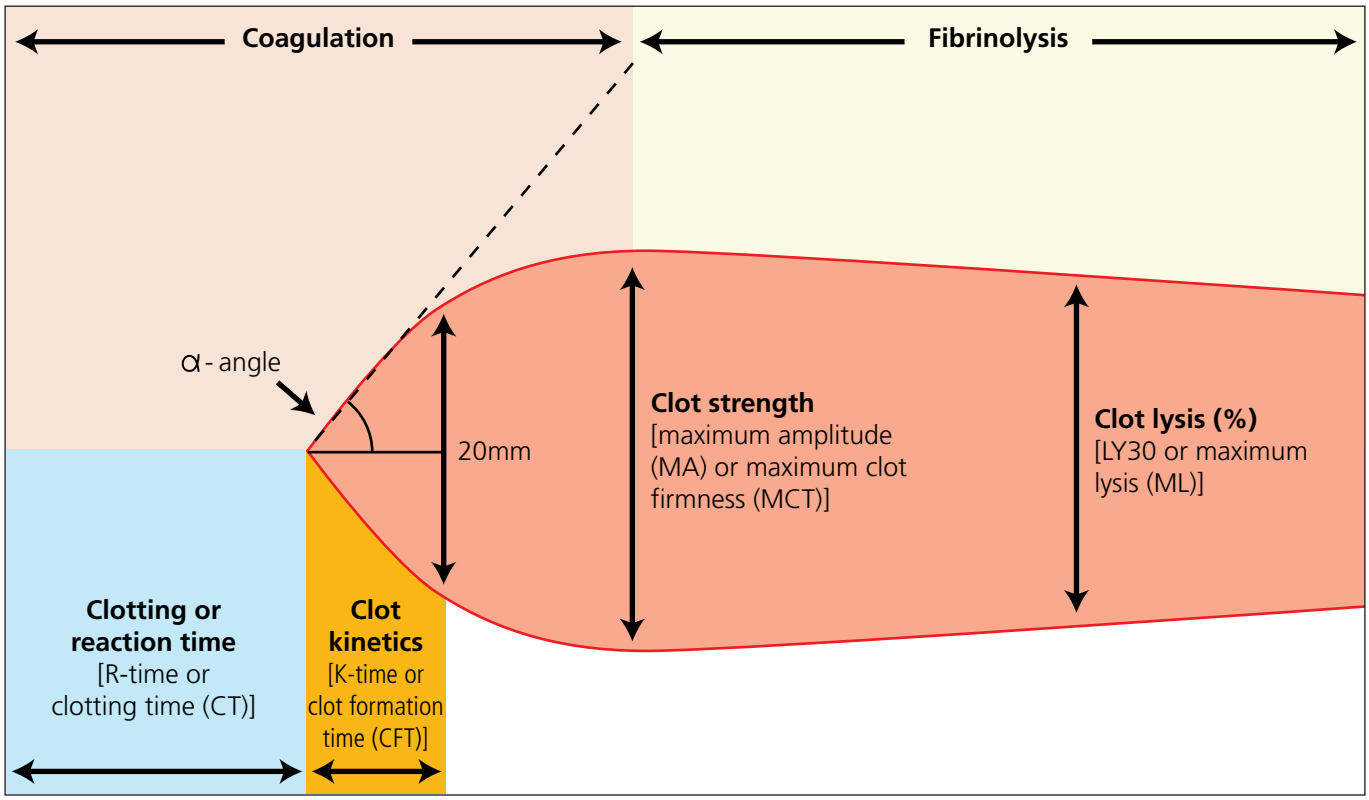
Background

Thromboelastography (or thromboelastometry) is a test of functional haemostasis, performed on whole blood, first described by Hartert in 1948. Unlike standard plasma based coagulation screens, the contribution of cell surface interactions, in particular platelet glycoproteins, is not excluded and the test probably better represents our current understanding of coagulation using a cell-based model. Thromboelastography assesses the kinetics of a forming clot, the clot strength and stability by measuring the viscoelastic properties of the clot. Careful interpretation of the data can differentiate whether excessive bleeding during or after surgery is induced by surgery or by abnormalities in haemostasis. In a rapidly changing clinical situation Thromboelastography (TEG) has the potential to improve clinical decision making by reducing delays and reliance on laboratory tests. Ultimately, when used effectively, TEG may result in a more timely intervention reducing the inappropriate use of blood and blood components.

Technology

There are two devices available that measure global haemostasis using the same basic principles but with slightly different technologies. In both devices whole blood is pipetted into a warmed disposable cup, a disposable pin is then lowered into the fluid blood. In the TEG® machine (Haemonetics Corp.) the cup is rotated every 10 seconds through an arc of 4°45' and the pin is initially stationary. As the first fibrin strands are formed the pin becomes tethered to the cup and starts to follow its motion. When maximum clot firmness is achieved the cup and pin move in unison. The motion of the pin is detected by a torsion wire linked to a transducer; hence a mechanical-electrical signal is relayed through a computer interface where real-time analysis is displayed. In the ROTEM® (Tem International GmbH), the cup is stationary and the pin rotates. Retardation of the motion of the pin by fibrin tethering is sensed through an optical-digital interface. In both systems a trace is produced with similar measurable parameters (figure 1). Native blood can be used, however, in order to speed up coagulation and give a more timely result, blood samples are usually activated.

Figure 1



Thromboelastography trace and measurable parameters: R (reaction time) or CT (clotting time): the period of time of latency from the time that the blood was placed in the cup until the initial fibrin formation; K or CFT (clot formation time) the speed to reach a specific level of clot strength; alpha (α) angle: measure of the rapidity of fibrin build-up and cross-linking (clot strengthening); MA (maximum amplitude) or MCF (maximum clot firmness): a direct function of the maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot.

Thromboelastography based transfusion algorithms

There are a number of studies, mainly in liver and cardiothoracic surgery, showing the efficacy of TEG based algorithms in determining blood component requirements. These algorithms are based on threshold values for particular TEG parameters, for example a prolonged R time or CT may indicate the need for Fresh Frozen Plasma (FFP), whereas platelet transfusion may be triggered by a low MA or MCF. A fibrinogen deficit may be detected by a low alpha angle in TEG® or by an abnormal Fib-TEM® test on the ROTEM®. Although limited in that TEG algorithms are based on "snapshots" and don't necessarily take into consideration all influencing factors and trends for an individual patient, their application has resulted in significant savings in blood component use.

Thromboelastography in major vascular surgery

The University Hospital of South Manchester (UHSM) has been utilizing TEG® analyses in cardiothoracic and intensive care settings for a number of years. More recently TEG has become standard practice in major vascular surgery, being used routinely in elective and emergency abdominal aortic procedures. Despite familiarity with the technique, some consultant anaesthetists remain sceptical of the test's clinical value. Review of our records reveals that in 232 patients undergoing elective abdominal aortic surgery, the TEG indicated the need for FFP in 36 patients. Of these, 11 (31%) were given FFP; 15 (41%) were not transfused immediately but were given FFP within 24 hours, and 10 (28%) recovered from surgery without any FFP being transfused. In the same group of 232 patients, the TEG indicated the need for platelets (MA<48mm) in 39 patients. This indication was followed in 10 (28%) patients, with a further 17 (47%) subsequently judged to have a clinical need for platelet therapy. The remaining 9 (25%) patients had no platelet transfusion within their hospital stay.

Conversely, of the 182 patients demonstrating normal R times at the end of surgery, 14 (7.7%) subsequently had an FFP transfusion. Similarly, 9 (4.8%) of the 184 patients with a normal MA at the end of surgery went on to receive platelets. These patients were likely to be those experiencing continued surgical bleeding postoperatively.

Our data illustrates that TEG data appears to be only acted upon around 30% of the time although a further need for blood components in the proceeding 24 hours may suggest its indications are accurate at least 75% of the time. Further analyses of our data may yield a more robust algorithm for blood component transfusion in this patient group.

Limitations and practical considerations

Although a point of care testing device, there are technical skills required to run accurate and reproducible TEG analyses. Sample quality is essential. Blood samples should be taken with great care to minimise platelet activation: the use of small gauge cannulae/needles should be avoided. Blood sampled from lines may also be at risk of heparin carryover if the sample is not taken correctly. In patients that are systemically heparinised, the underlying clotting profile can be assessed by using cups and pins coated with heparinise. Timely handling of non-citrated whole blood samples is also important as the test needs to be started within four minutes to avoid initiation of clotting in the sampling tube. Quality control is imperative, not only to validate the function of the machine but also to test the competence of the operator. Another key skill relates to interpretation of the TEG trace: the test should not be viewed in isolation but more properly put in context with the overall clinical picture. It is particularly important to take a baseline sample to show any changes which may be more important than absolute values.

Both TEG devices use kaolin activation of clotting through the intrinsic pathway of coagulation, the ROTEM® additionally uses tissue factor activation via the extrinsic pathway (ex-TEM® test). Activation through these pathways results in a potent thrombin burst which overwhelms all other platelet activation pathways. This means that the effects of antiplatelet drugs such as aspirin and clopidogrel are masked in standard thromboelastography and this should not be ignored when interpreting results. A more specialised TEG analysis has been developed to elucidate the effects of anti-platelet drugs (Platelet mapping™), but this is more technically challenging and probably needs further evaluation and validation before it comes into standard practice.

Summary

When used correctly, Thromboelastography is a useful tool in determining blood component requirements. As familiarity and confidence in the technique grows, it may be possible in future to refine TEG based algorithms to incorporate changes in coagulation to further individualise blood product therapy in the surgical patient.

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Pathogen Reduction Technologies

In the privileged part of the planet, where readers of this newsletter congregate, blood transfusion is probably very safe. Testing, donor exclusions, and low infectious disease burden in the population seem to deal with the microbiological ecosystem that blood transfusion gives rise to. Transfusion may not be safe of course - unrecognised diseases with long silent periods can spread for years before they are recognised or understood as happened with HIV, and vCJD remains a serious concern. Nevertheless, for viruses, bacteria and protozoa we're in reasonably good shape, though there are residual problems:

- window period transmissions of the diseases we test for;
- transmissible diseases in our donor population that we don't, or don't always, test for - CMV, parvovirus B19, malaria;
- occasional intruders - West Nile fever, Chikungunya, dengue, Chagas' disease, babesiosis, Crimean Congo fever, Rift Valley fever, SARS, influenza;
- transfusion-transmissible agents that emerge from time to time to cause fear, alarm and sometimes disease - monkeypox, simian foamy virus, XMRV.

Vigilance for and reactions to these problems cost large amounts of money, and are not foolproof. In the developing world, these problems are present in different orders of magnitude, and effective defence is phenomenally difficult to achieve.

Any sterilisation technique for blood components that was affordable (both for rich and poor countries), effective, did not damage the therapeutic cells or proteins, and was not toxic to recipients, would achieve rapid acceptance. This goal has not been reached, but there are some promising developments.

There are effective techniques for pathogen reduction (PRT) in plasma for transfusion. Solvent-detergent treatment of plasma pool units has been in clinical use for almost twenty years, and offers very good protection from disease transmission, with protection from transfusion-related acute lung injury thrown in for good measure. Methylene Blue treatment is also safe and effective, and perhaps cheaper. Amotosalen and UV light treatment can, like methylene blue, be applied to single units of plasma, and is becoming established in some centres.

Platelets can also be treated effectively with amotosalen and UV light, or with riboflavin and UV light. Both treatments exert their effects through binding to DNA or RNA; energy transfer to the molecules from the photons of UV light causes covalent cross linking in the viral ribonucleases, rendering them incapable of replication. In the case of amotosalen, a psoralen, the parent compound is toxic; excess in the platelet or plasma unit has to be removed. The process also damages elements of the therapeutic product: mitochondria in platelets are damaged, and the photo-energy is absorbed by proteins and membranes in the plasma and the cells, causing some loss of function. It remains to be seen whether the losses of product and activity in platelets can be tolerated without loss of clinical efficacy, or whether they can be compensated for by increasing the dose transfused.

There are other pluses for PRT of platelets: no need to test for bacteria, an expensive, wasteful and not completely effective technique, no need to irradiate - PRT prevents T-cells replicating too, and no need to worry about CMV status. One might also consider dropping travel deferrals for platelet apheresis donors in the setting of pathogen reduction.

But we will not be able to reap the full benefits of PRT until red cells, or even whole blood collections, can be treated. Chemical agents that work for platelets and plasma should work for red cells; the problem is effective penetration of the red cell suspension with photo-energy to ensure pathogen kill. Two approaches are under development - use of chemical agents that do not require photo-activation, and using additional processes in red cell or whole blood preparations that allow energy penetration. Clinical trials are either beginning or are planned. In the past, small clinical trials of two chemical approaches - S303 made by the Cerus Corporation and Inactine made by Vitex, were halted when unexpected red cell antibodies developed in a small number of recipients. Vitex have subsequently folded their tents, but Cerus are optimistic for the future of their approach.

Pathogen reduction of red cells, platelets and plasma, would not mean the end of all testing. NAT could be done in larger pools, serology for HIV and hepatitis C and CMV could go. HTLV I/II testing, hepatitis B core antibody testing and bacterial testing for platelets could also go; irradiation can be dropped, and testing or deferrals for malaria, Chagas', WNV, dengue, Q fever, Chikungunya and babesiosis could also be abandoned. Concerns around new agents like XMRV would focus instead on efficacy of removal rather than strength of disease association. The pathogen kill of current technologies is not limitless, probably in the order of 10^6 for most enveloped viruses, and considerably less for non-enveloped ones. Breakthrough for high viral loads may occur, especially in ramp-up early phases of infection. We will still have to worry about parvoviruses, hepatitis A, and any evolving non-enveloped viruses that our accidental ecosystem allows to emerge. Spore-forming bacteria may escape destruction, and prions will be unaffected.

Eventually PRT may become the standard for blood components in the developed world; costs will fall and misgivings will be overcome. Several European countries have already moved over completely to pathogen-reduced plasma, and a number of others are seriously engaged in adopting or appraising PRT for platelets. For less privileged countries where infection is a far greater risk and costs are a far greater problem, PRT will require a different commercial model to ensure fair return for the manufacturers. Nevertheless, overcoming the enormous difficulties involved would be well worth the effort.

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I declare that I have no personal interest, direct or indirect, in any of the companies or products mentioned in this article.

The Advisory Committee on the Safety of Blood, Tissues and Organs – An Update

The Advisory Committee on the Safety of Blood, Tissues and Organs remit is to 'advise ministers of the UK Government and Devolved Administrations as well as UK Health Departments on the most appropriate ways to ensure the safety of blood, cells, tissues and organs for transfusion/transplantation'. In April of this year, the Advisory Committee met for the tenth time since its inaugural meeting in January 2008. An overview of SaBTO and the framework which it uses to formulate its advice was published in the Autumn 2008 issue of *Blood Matters*; however since that time SaBTO has considered a number of issues that affect the safety and sufficiency of blood, cells, tissues and organs.

The workings of SaBTO

The quarterly meetings of SaBTO represent only a small proportion of the work which this body of experts perform when considering safety and sufficiency issues relating to transfusion and transplantation. Much of the work of SaBTO is conducted by short-life working groups which consider each item in great detail. These working groups, which are chaired by committee members, consist of both SaBTO representatives and external individuals with relevant expertise. The use of these working groups not only allows SaBTO to consider each individual issue in great depth, but also to call upon the advice of external experts. Recommendations made by a working group are then considered by the Advisory Committee at its quarterly meetings. This approach has allowed SaBTO to look at a wide range of issues in its short life time.

Public Meetings

SaBTO has also chosen to actively engage with the public because many of the issues it considers are of significant public interest. This engagement has been

through both consultations and an annual public meeting. The topics chosen for the two public meetings to date have been "vCJD and Blood" in 2008 and "Blood Donation - selection, deferral and exclusion" in 2009. The meetings, which were open to anyone, were well attended and have generated considerable discussion. The 2010 public meeting, which will take place in October, will be on risks associated with the use of marginal organs.

A FLAVOUR OF CONSIDERATIONS TO DATE

Risk reduction measures for vCJD

Many of the interventions which SaBTO has considered are related to the risk of secondary transmission of vCJD posed by blood components and tissues. The measures considered to reduce this risk include importation of red blood cells and plasma from a low-risk country, increased component donation (apheresis platelets and double dose red cells (DDRC)) and prion filtration of red blood cells. All of these measures have the potential to reduce the risk of vCJD transmission. However, the framework used by SaBTO takes into account many factors including cost, safety, impact on supply, relative benefit and value for money, consequently recommendations cannot be made on risk reduction alone. SaBTO has also chosen to stratify transfusion recipients into three distinct groups when considering certain measures. These groups are:

1. Children (under 16)
2. Haemoglobinopathy patients
3. All other patients

Children are considered separately because those born after 1st January 1996 will not have been exposed to BSE through their diet, whereas haemoglobinopathy patients have significantly increased donor exposure due to their transfusion dependency.

SaBTO did not recommend the introduction of universal importation of red cells due to potential problems with supply; however it has recommended universal importation of fresh frozen plasma (FFP) from a low-risk country. SaBTO has also recommended the use of DDRC for children and haemoglobinopathy patients as well as the use of prion filtered red blood cells for children. In addition, SaBTO has endorsed the target of 80% apheresis platelets set by its predecessor MSBTO.

The SaBTO recommendation on the importation of FFP is currently undergoing an impact assessment in the Department of Health. Similarly, the recommendations on DDRC and prion filtration are undergoing an impact assessment, but these have been combined due to the large overlap between them. The impact assessments are designed to identify the complete impact on the NHS of implementing a SaBTO recommendation and they highlight the total net benefit (or cost) of implementation. Once complete, the impact assessments are submitted for consultation, after which time they are considered by the Ministers of Health, who may issue an instruction to implement. In many ways, a recommendation by SaBTO represents a single, but critical leg of a journey towards implementing a new measure. It is also worth noting that SaBTO advises the entire UK but impact assessments are performed for the individual countries which make up the UK. It is highly likely that many of the recent recommendations made in relation to vCJD risk will reach the stage where an instruction is received from the Minister.

Risk reduction measures for bacterial contamination of platelets

The introduction of improved arm cleansing and diversion of the first 20ml of a donation into a separate pouch have significantly reduced the risk of bacterial contamination of platelets. However, a number of additional technologies, including bacterial screening and pathogen inactivation are available which reduce this risk further. Having considered the findings of its Platelet Working Group, SaBTO did not recommend the implementation of either technology. Interestingly, three of the four UK blood services currently perform bacterial screening and the 4th (NHSBT) has recently decided to implement it. This discrepancy between the SaBTO recommendation and current practice in the UK Blood Services highlights the different pressures that they are under.

Current Topics under review

The work load of SaBTO continues to be extensive. This year its expert members and working groups will consider issues as far reaching as consent for blood transfusion, donor deferral and exclusion, processing of femoral heads used in hip revision surgery, the use of organs from donors with central nervous system tumours, the microbiological safety of organs, tissues and cells used in transplantation and the use of cryoprecipitate. These will be considered by topic specific working groups Chaired by SaBTO members.

Consent for Transfusion

The issue of consent for blood transfusion has been discussed on several occasions by SaBTO, with the committee expressing some major concerns, including that:

- Patients are not being given information on risks, benefits, and alternatives to transfusion;

- Patients are not given the right to refuse transfusion;
- Patients may not be aware they have received a transfusion;
- Patients who receive blood may go on to donate blood, without realising that they should not;
- There is inconsistent practice across the UK.

In order to address these concerns, a SaBTO Working Group, lead by Catherine Howell, (SaBTO Member and Chief Nurse Patient Services, NHSBT), launched a public consultation on "Patient Consent for Blood Transfusion". Launched on 3rd March 2010, this consultation is to provide evidence for formulating advice.

The committee has made clear the importance of considering emergency cases and elective procedures where transfusion may or may not be required and are also mindful of the operational impact of any changes. However, they are keen that patients receive standardised, consistent information about the risks and benefits of transfusion. The committee also believe that patients should be informed about the alternatives to blood transfusion if appropriate.

The SaBTO consultation closed on 27th May 2010 with the aim of identifying the preferred option for recording consent, exploring the operational impact of implementation and confirming what type of information patients should receive.

Donor deferral and exclusion

In 2009, the topic of the SaBTO public meeting was *blood donor selection, deferral and exclusion,* with a particular focus on the current policy of excluding from donation men who have ever had sex with another man (MSM). As part of its assessment of the current blood donor selection, deferral and exclusion criteria, SaBTO has begun a review of this policy. The committee is mindful of the fact that a balance can be struck between safety and fairness and are mandated to take decisions based on evidence, not on political considerations. Any change to the current policy must be accompanied by clear evidence that safety will not be compromised.

SaBTO has committed to reviewing the current policies, once the results of research on donor attitudes to compliance become available. The review, which will be conducted via a working group composed of representatives from multiple stakeholders including patient groups, HIV charities, LGBT groups, blood transfusion services as well as experts in haematology, epidemiology and virology, is expected to report late 2010.

The committee is not the only body currently reviewing these policies. The European Committee on Blood Transfusion of the Council of Europe have created an ad hoc group of experts aimed at *"monitoring current practices and defining a harmonised approach to establishing rules for donor deferral linked to risks attributable to sexual behaviour"*. This group are expected to present the data they have collected by the end of 2010 and it is highly likely that their experience, together with that of countries that have recently changed their donor deferral policies will inform the review currently being undertaken by SaBTO.

Guidance on the microbiological safety of human organs, tissues and cells used in transplantation

In 2000, the predecessor to SaBTO issued its guidance on the *Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation*. Since that time, there have been considerable changes to the regulatory landscape. For example, the Human Tissues Authority (HTA) now regulate the removal, storage and use of tissues for human applications and European Tissues and Cells directives became law in the UK in 2007. As a result of these and other changes, SaBTO has undertaken an extensive review of the previous Guidance. The updated Guidance is currently out for extensive consultation and a final version is anticipated in the middle of 2010.

And finally

The issues which SaBTO considers are both varied and complex. The committee can only undertake and fulfil its' extensive workload thanks to the continued commitment and dedication of its expert members.

Further information relating to SaBTO and public summaries of its meetings can be found at http://www.dh.gov.uk/ab/SaBTO

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Enhancing Patient Care; Framework for Safe Blood Transfusion Practice

The governance Framework document outlining guidance for nurses and midwives wishing to extend their role to prescribe blood components was launched at the British Blood Transfusion Society (BBTS) 2009 Annual Scientific Meeting.

The Framework document began as a collaborative project between NHSBT and the SNBTS, which explored the feasibility of registered practitioners other than doctors, prescribing blood components. Anecdotal reports of fragmented care, treatment delays and safety issues for patients requiring blood, suggested we should examine other ways of delivering transfusion care. Since 1996 the serious sequelae of blood transfusion has been recorded by the Serious Hazards of Transfusion (SHOT) reporting scheme. The largest number of incidents reported, is in the incorrect blood component transfused category, 60% of all reports. It became apparent in 2001 that there were cases where patients had received inappropriate or unnecessary transfusions. There have been a total of 384 such reports and two patients have died from unnecessary transfusion. SHOT have highlighted that junior doctors were making critical decisions without adequate basic knowledge or experience (SHOT 2008).

As a first step a UK wide survey canvassed the opinion of nurses and doctors on whether other registered practitioners should prescribe blood. Sixty percent (60%) of respondees were supportive. The survey also identified that in several clinical specialties nurses were already undertaking most of the aspects of transfusion care; they assessed the patient's clinical needs and transfusion requirements, influenced the decision to transfuse, made referrals and admission arrangements but were unable to actually prescribe the component. These practitioners have developed their knowledge and reported that they would like to use their expertise to benefit patients.

To clarify the legal situation on role development in this area of practice, advice was sought from both the Royal College of Nursing (RCN) and the Medicines and Healthcare products Regulatory Agency (MHRA). The advice received is summarised as:

> Section 130, 1968 Medicines Act has been amended by regulation 25 of the Blood Safety and Quality Regulations 2005 (SI 2005 no 50). The effect of this amendment was to exclude whole human blood and blood components from a legal definition of a medicinal product. Therefore there are no legal barriers to other appropriately trained competent registered practitioners ordering and authorising blood.

As good governance is central to all advanced practice, it was suggested that a governance framework document was developed to support practitioners who wished to undertake this role. A multidisciplinary workshop took place in October 2008 to consult on the content of the document. The workshop was attended by representatives from the Royal College of Nursing (RCN), Nursing Midwifery Council (NMC), Royal College of Midwives, British Blood Transfusion Society, Serious Hazards of Transfusion (SHOT), Department of Health, the British Committee for Standards in Haematology, BBTS Professional Affairs and Education Committee, National Blood Transfusion Committee (England), Regional Transfusion Committee (Northern Ireland), the Welsh Clinical Advisory Group and interested individual practitioners. The consultation period was extensive and the final document was well received by all the major key stakeholders. The framework sets out clearly defined guidance to provide safe patient care around:

- patient selection, which should be governed by local needs
- selection criteria for practitioners, to ensure the most appropriate care for patients
- indemnity issues, to protect patients as well as practitioners
- education and training, to support role development
- clinical governance procedures, which must be in place to support practice
- practitioner, medical consultant and management responsibilities, to ensure clarity and delineation of roles, which must include supportive frameworks
- informed consent, to protect patients
- safe and appropriate practice, to be supported by national and local guidelines
- reviewing and monitoring practice, to ensure compliance with national and local guidelines as well as monitoring improvement to local services.

There are a number of challenges to implementing this initiative such as the lack of an established formal education programme. This is similar to nurse role development in other areas of practice e.g. the 'Hospital at Night' practitioner. In these areas educational needs were met by the individual practitioner working with a clinical mentor within their specialty to identify their learning needs and developing a learning plan to meet any knowledge gaps. The practitioner then develops a portfolio of evidence to demonstrate that competencies

have been met; in addition there is also a period of mentorship and clinical supervision. This is the approach that is suggested in the framework. However since the document was launched, preliminary work has been undertaken by the Scottish Government Health Department (SGHD) to look at the feasibility of developing some type of multi-professional educational support for practitioners. The time-frame for delivering this initiative is currently being established but will take some time to complete.

The concept of patient-centred care is critical to the pursuit of high-quality service provision and this project has shown that there is a service gap for patients who require blood transfusion support. To date the clinical areas that have shown interest in piloting this role development are specialist areas (e.g. Haematology, Neonatology and Intensive Care). The nurses within these areas are experienced, senior nurses working at advance practice level and we do not envisage this changing in the short term. By using the untapped knowledge and expertise of these experienced practitioners there is the potential to greatly improve the patient's transfusion experience.

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Link to Governance Framework website:
http://www.transfusionguidelines.org.uk/docs/pdfs/BTFramework-final010909.pdf

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Developing an Online Blood Ordering System (OBOS) – A New Approach

Over the last few years discussion with customers clearly identified the need for NHSBT to improve the ordering system for blood and blood components. The existing system relies on orders being faxed with all the associated inherent problems and is characterised by:

- poor fax quality
- manual transcription errors
- an incomplete audit trail
- no acknowledgement notification that the order has been received or dispatched
- failure to identify delays or problems with the dispatch of an individual order
- no national overview of order activity
- planning assumptions based on what is issued and not what was originally ordered
- poor benchmarking against other important suppliers to the NHS on order placement.

NHSBT also needed to improve its customer involvement in decision making and speed up its response to customer needs. For this project it was decided to adopt an iterative or 'Agile' approach to software development, following the successful use of this approach to implement the Electronic Offering System (EOS) at Organ Donation and Transplantation. This radically different approach significantly reduced the time taken to deliver a new IT system and involved stakeholders throughout the development process. The Online Blood Ordering System (OBOS) project was the first time the approach had been used when NHSBT's Pulse computer system needed to be included in the process.

At an intensive two-day workshop the key stakeholders worked together to define the scope and functionality of the new ordering system. Continual testing of the system during development reduced the need to re-write parts of the specification and the risks of deviating from the scope. The stakeholders, including hospital staff, were involved throughout the process. The hospitals invested a lot of time in the workshop and user acceptance testing and their enthusiasm was inspiring.

Two external IT companies were involved in the project: Savant which holds the tendered contract for the maintenance and development of NHSBT's Pulse computer system, and Sapient which delivered the detailed design specification and is experienced in the 'Agile' development approach, having developed EOS for Organ Donation and Transplantation.

The Workshop

Attendees at the 2 day workshop

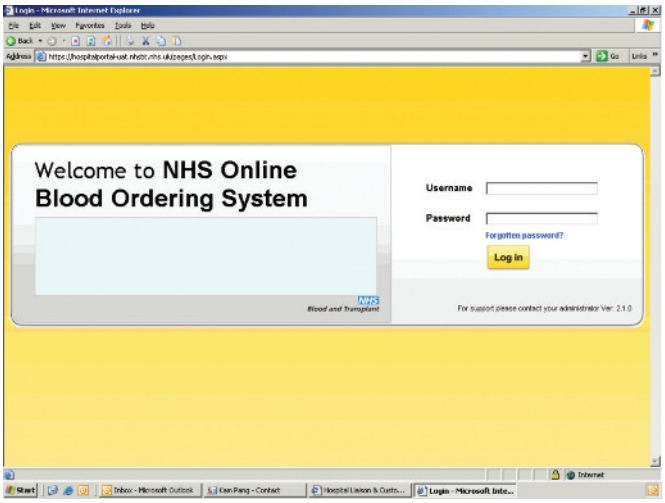
In preparation for the workshop on 31st March - 1st April 2009, Sapient conducted interviews with a range of NHSBT and hospital staff. The primary purpose of the interviews was to determine which issues to focus on at the workshop and subsequent sessions. The interviews revealed strong support for the initiative, and indicated that hospital personnel needed the most input in order to deliver a usable solution.

The workshop was an excellent opportunity for hospital laboratory staff to meet staff from NHSBT, Savant and Sapient. The pace of the workshop surprised the 24 participants and an enormous amount was achieved in two days of intensive brainstorming. The session facilitated rapid communication and reassured us all that the important decisions being made were led by the people who would be using the new system.

The main aim of the workshop was to define business requirements for the system. Various techniques were used including the mapping of current processes, identification of known 'pain points' in these processes, and open brainstorming sessions on future priorities and requirements. In addition, prototyping sessions were conducted to enable users to indicate their preferences regarding the layout of the ordering screens. A key objective for the workshop was to identify users' needs and priorities both for a pilot application of the system and for the longer term.

The Pilot

OBOS "Log in" screen



The Online Blood Ordering System (OBOS) was ready to pilot in February 2010.

Five hospitals took part in the pilot:

- John Radcliffe Hospital which is supplied by NHSBT Oxford
- Freeman Hospital which is supplied by NHSBT Newcastle
- Charing Cross Hospital which is supplied by NHSBT Colindale
- Royal Brompton Hospital which is supplied by NHSBT Colindale
- Darent Valley Hospital which is supplied by NHSBT Tooting.

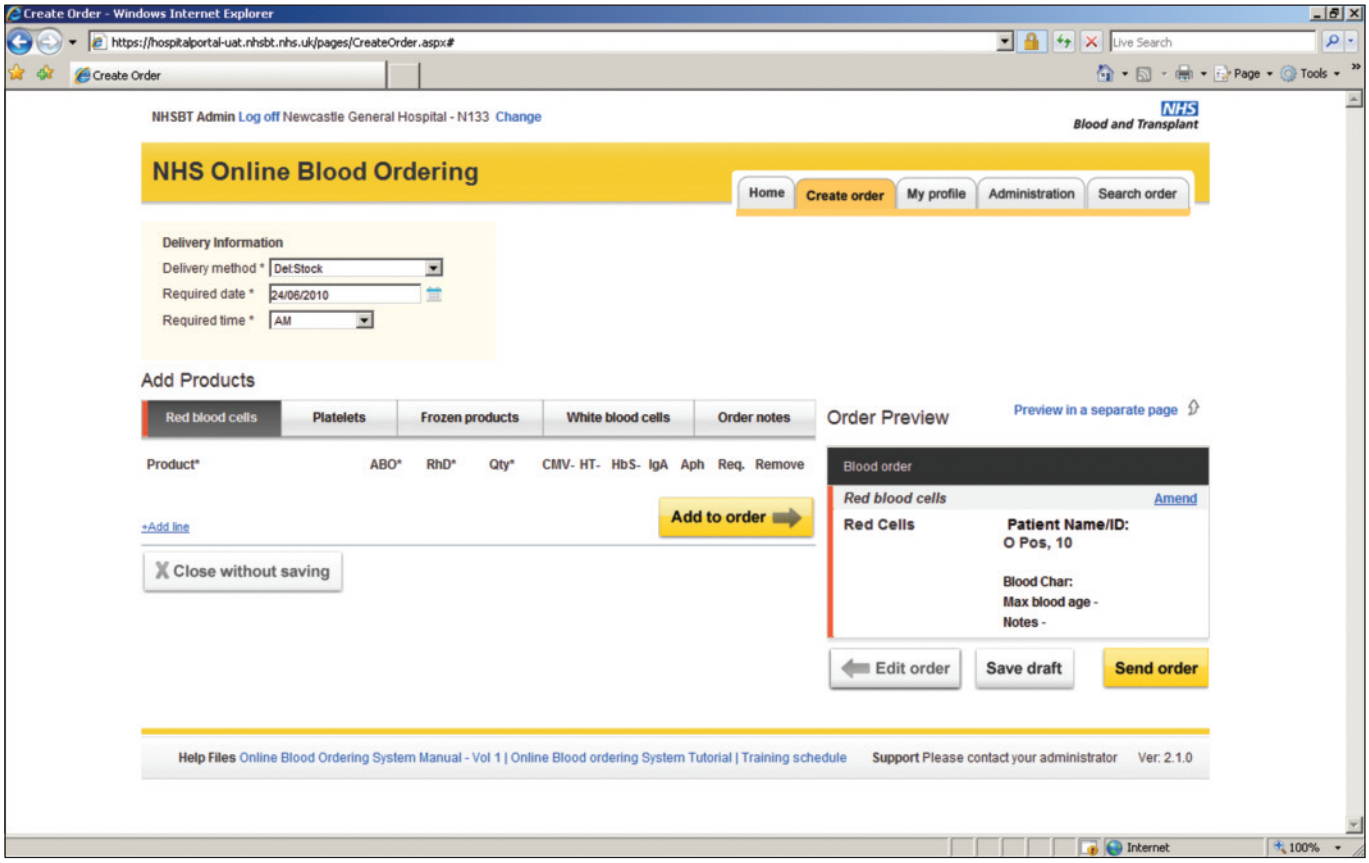
Feedback from users at the pilot hospitals was positive:

"Easier then faxing - I love it."

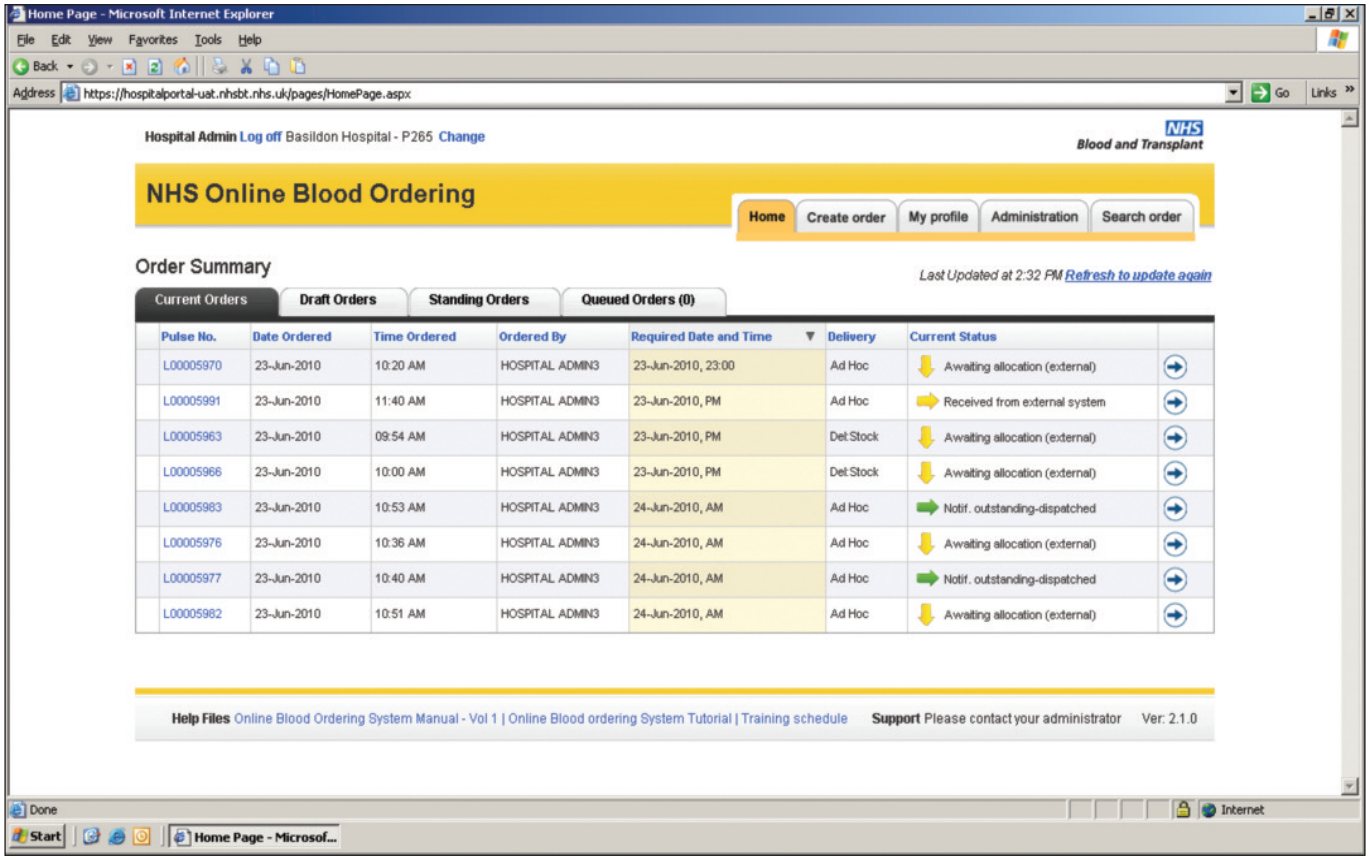
"Easy to use, just like on line shopping really."

NHSBT Hospital Services staff also felt that OBOS was the way forward and would bring blood ordering systems into the twenty first century. The pilot successfully identified 'bugs' and improvements required for the planned full national implementation. A phased approach to the roll out began in June 2010 and will see OBOS rolled out to 307 hospitals across England and North Wales. Training sessions for hospital staff on how to use the new system will enable approximately 25 hospitals to 'go live' each month, concluding in September 2011.

The OBOS "Create order" page



The OBOS "Home" page



The many benefits for full roll-out of OBOS to all hospitals include:

- a more efficient and accurate ordering process:
  - reduced time and effort involved in submitting and registering an order
  - reduced transcription and interpretation errors
  - fewer telephone calls
  - capture of 100 per cent of orders and order details
  - prevention of the issue of platelets that expire before the time required.
- hospitals are able to track orders including details of split orders, substitutions etc and can see when 'collect' orders are ready
- robust audit trail for hospitals
- positive transfer of information i.e. no lost faxes
- does not rely on fax machines being maintained (ink, paper etc)
- lower cost for online service channels than fax
- one system rather than three separate order forms
- new products easily added to the system
- robust, standardised national process for standing orders
- NHSBT will base stock management and planning on demand not issue data
- improved customer service.

In conclusion, this has been a highly successful project in which NHSBT has worked closely with hospitals and two IT companies to rapidly produce a bespoke online ordering system. The users of OBOS at the hospitals and NHSBT were engaged in the planning from the outset to produce a system that works well for them and hasn't been imposed by 'planners' who don't understand the intricacies of the operational environment. The pilot and full national implementation of the system are just the beginning; OBOS presents exciting opportunities for further collaboration between hospitals and NHSBT.

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In Vitro Generated Red Blood Cells for Transfusion

A call for proposals from the American defence department (DARPA) first prompted us to consider the potential of *in vitro* red blood cell production as a replacement for donor based services. Their challenge was to develop a battle-field based unit that could generate red cells, initially from limited-capacity adult stem cells but ideally from self-renewing, sustainable pluripotent stem cells. We were unsuccessful in our application to DARPA but, driven in no small part by the irrepressible Drs Willie Murphy (IBTS) and Marc Turner (SNBTS), we re-focussed our efforts towards the more universal issues of providing a secure blood supply for the future.

Problems of sustaining red blood supplies for the future

The problems involved in maintaining a reliable supply of red blood cells are familiar to most of us; even the most well-developed blood services face a number of fundamental issues. The first of these is insufficiency of supply. Even in developed countries such as the UK, maintenance of donor numbers is problematic, due to demographic, social and cultural changes and the increasing stringency of national and international regulatory requirements. The second, is the persistent threat of transfusion transmissible infections (TTI). Though the risk from HBV, HIV and HCV is currently well managed, there are many 'new' threats to the blood supply including known infectious agents which now spread more easily across international boundaries due to climate change and the growth in international travel (e.g., West Nile Virus, Chikungunya Fever) and new emergent infectious agents of uncertain pathogenicity. Third is the problem of immune incompatibility. Donor and recipient matching by blood banks can lead to delayed blood supply in an emergency and are a source of laboratory and clinical error. Incorrect blood component transfusion remains the major cause of morbidity and mortality in the UK (SHOT 2006).

These problems, of course, pale into insignificance compared to those in the developing world. Developing and transitional countries are home to 80% of the world's population but collect only 45% of the global blood supply (WHO statistics). These countries bare the heaviest burden of disease (and therefore the greatest requirement), and also face the greatest challenges in terms of ensuring blood safety, often with high prevalence of TTID amongst the putative donor population and a paucity of infrastructure.

In vitro generated red blood cells as an alternative to donor-based supplies

It would be extremely valuable, therefore, to develop a potentially limitless, infection free, immune neutral source of erythrocytes for transfusion. It has been shown that erythrocytes can be generated *in vitro* from haematopoietic stem/progenitor cells (HSPC) from bone marrow or umbilical cord blood, however it has not, as yet, proved possible to expand human HSPC in culture and numerous donors would still be required. Therefore this source does not circumvent the problems outlined above. Human embryonic stem cells (hESC), in contrast, have seemingly limitless proliferative capacity and the potential to differentiate into the majority of adult cell types including HSPC and erythrocytes.

There are a number of barriers to the development of clinical cellular therapeutics from hESC (Box 1), and to date there are no hESC-derived therapies in clinical trial. However, most of these problems are circumvented in the generation of erythrocytes (Box 2) and if possible, therefore, that red cells could be amongst the first hESC derived cellular therapeutics to reach clinical application and that there is a clear and present clinical need for such a product (Mountford, *et al* 2010).

Box 1

Concerns over clinical use of hESC

- Mainly mixed differentiation, still need to refine
- Potential for teratoma formation from undifferentiated hESC
- Small experimental scale, need to scale-up
- Off-the-shelf therapy would still require huge bank to tissue match, otherwise immune rejection issues
- Animal products used in culture, infection and immune risks

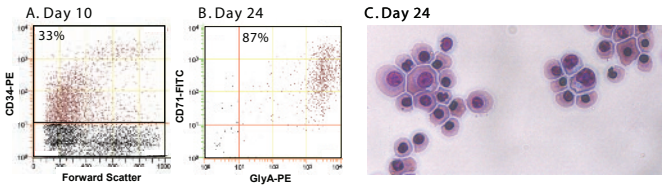
Box 2

RBCs derived from hESC have many advantages compared to other SC-derived therapies

- Differentiated cells enucleated – no risk of de-differentiation or teratoma
- No significant MHC expression – no classical rejection (use O RhD- cells)
- Average life-span of cells only ~ 120d
- Final product can be terminally sterilised to destroy pathogens & remnant RNA/DNA
- Single cell type sufficient for therapy
- Delivery iv to peripheral vein – not into complex organised tissue (cf: brain)
- Established application (50 yrs) with associated assays, protocols and standards

In addition to the issues common to all hESC-derived cells there are some specific challenges to the production of RBCs in the laboratory. One of the main benefits of hESC is that they can make cells of all lineages, however they are very prone to do just that and it is very difficult to direct their differentiation to generate specific lineages. We enhance their commitment to HSPCs using either stromal co-culture or growth factor supplemented liquid culture, and were initially able to generate cultures containing around 10% HSPC. We have subsequently increased this average to around 40% HSPC that proliferate and differentiate into haemoglobinised erythroblasts (Figure 2). However, these cells must undergo many more steps during their maturation from erythroblasts to reticulocytes and eventually enucleated erythrocytes. Additionally, as hESC are derived from embryonic tissue the cells must also undergo sequential globin switches from embryonic ζ-chains, to foetal γ-chains and finally to adult β-globin.

Figure 1



Human embryonic stem cell differentiated in liquid culture to HSPC (A. Day 10) and later to erythroid series cells (B, C. Day 24; cytospin with Romanowsky stain)

In order for the final RBCs to be clinically useful all of the processes used must be compliant with current Good Manufacturing Process (cGMP) including the initial hESC derivation, maintenance, differentiation, maturation and processing protocols. We (Roslin Cells) have derived a new hESC line under fully cGMP certified conditions and we have to adapt all of our research protocols to these rigorous standards. It has recently been decided that cell therapies will be classed as advanced therapy medicinal products (ATMP) and regulated by the European Medicines Agency (EMEA) and the Medicines and Healthcare products Regulatory Agency (MHRA) and the Gene Therapy Advisory Committee (GTAC) in the UK.

Finally, there is the issue of cell numbers. A single unit of RBCs contains $2x10^{12}$ cells, and 2.2 million units are transfused per year in the UK, therefore to meet the UK's annual needs around $4x10^{18}$ cells would be required. Globally, approximately 80 million units containing around $1.6x10^{20}$ cells/year are currently administered and much of the world's need remains unmet. These cell numbers are greatly in excess of those used in current industrial systems and therefore, it seems inevitable that novel bio-manufacturing processes will be required for *in vitro* derived red blood cells to become a globally viable

product and there will be significant cost implications in the early development of these facilities.

However, despite the challenges we remain certain that *in vitro* RBC manufacturing can provide a new source of safe RBCs for worldwide use. We have assembled a uniquely skilled team including the University of Glasgow; MRC Centre for Regenerative Medicine, University of Edinburgh; Roslin Cells and the UK and Irish Blood Services (Box 3); with the capability to deliver this vision. We have started work on a Proof of Principle study under a Strategic Translation Award from the Wellcome Trust Technology Transfer scheme, and are cautiously optimistic that we and others can move towards the routine supply of universal donor O RhD- red blood cells as an off-the-shelf solution that is available throughout the world even in areas where donor services are not currently operative.

Box 3

Proof of Principle Project team

Prof Marc Turner, SNBTS/MRC Centre for Regenerative Medicine, University of Edinburgh

Dr Joanne Mountford, SNBTS/University of Glasgow

Dr Lesley Forrester, MRC Centre for Regenerative Medicine, University of Edinburgh

Prof David Anstee, NHSBT, Bristol

Prof Paul de Sousa, MRC Centre for Regenerative Medicine, University of Edinburgh & Roslin Cells, Edinburgh

Mr Aidan Courtney, Roslin Cells, Edinburgh

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Landsteiner Meets Haldane: ABO Antigens as Another Red Cell Adaptive Frontier in Malaria

Plasmodium falciparum, the parasite which causes the most lethal kind of malaria known to humanity, has co-evolved at breakneck speed with us, from well before the hominid divergence from chimpanzees. The ABO blood group system also predates our own speciation by millions of years, and ever since the days of Landsteiner, has been appreciated as the first and most commanding presence in the history of blood transfusion. Malaria and ABO begin by having primordial origins in common with each other, but does the relationship go deeper than this? Many lines of evidence would suggest that the answer to this is a resounding yes, and that our specialized knowledge in the transfusion laboratory may play a novel future role in how we approach this disease, which claims more lives now than ever before.

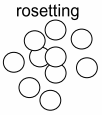
If we try to imagine how ABO could matter in our relationship with a pathogen, there are several possibilities: there may be differences in how the various ABO antigens on cells are invaded or exploited – and how free ABO antigens may mitigate these encounters ("forward type" relationships), or there may be differences in how the various ABO isohemagglutinins interact with or neutralize the pathogen itself ("backwards type" relationships). The mechanism by which the advantageous ABO type gains ascendancy in the population is revealed either by who survives by virtue of not getting the infection at all (which would be proof of effect by counteracting infectivity), or by who survives by easing the disease's severity (which would be proof of effect by minimizing pathogenicity). In looking at

whether ABO distributions are different among those who are and who are not parasitaemic, we do not see a relationship… but in looking at who gets severe versus uncomplicated disease, the difference is clear: Blood group A appears to suffer the severest manifestations of the disease, while group O is enriched among those whose malaria remains uncomplicated. This implies that group A, our most ancient wild-type, is assailed and perhaps rooted out, while group O, the mutant, is spared and permitted to rise in prevalence.

Borrowing from the fruitful observations of JBS Haldane, in whose wake the overlap of thalassaemias and malaria endemicity led to studies on exactly how the trait (or the population's "balanced polymorphism") bestows its survival advantage, we likewise take stock in ascertaining that the ratio of groups O to A exceeds unity in many of those same parts of the world. The following in vitro, microscopic examination of this enormous geo-evolutionary clue showed something peculiar: That the malaria-infected red blood cell (iRBC) "rosetted" (adhered) with uninfected red blood cells (uRBC) best when they were group A, and least when they were group O, while these rosettes were disrupted with the addition of free A antigen, or prevented if A antigens were enzymatically cleaved off pre-emptively. The plot thus thickened, not only for those with group O as a red cell type, but for those with weaker A red cell types, and for those group A's with the highest concentration of free A antigen by virtue of their Secretor or Lewis types.

What is the significance of more versus less rosetting? Rosetting is one of two kinds of cytoadhesion, wherein iRBC attach to other host cells to stall their flow in the bloodstream. (The other kind of cytoadhesion is "sequestration," where the iRBC attaches in a pseudoleukocytic fashion to the endothelial cells of the microvessels.) The parasite is clever for not only choosing to inhabit red cells, which are HLA-invisible food-factories and sanctuaries all at once, but for figuring out a way to subvert these cellular tanks to arrest their flow, so as to avoid circulation into the ever-critical spleen where they are certain to otherwise fail the test of passage through its phagocyte-policed and tightly fenestrated sinusoids. Cytoadhesion is thus the parasite's way of getting the iRBC around all the many ways humans have evolved to make their red cells more sensitive to early clearance in the spleen, inclusive of the traits which genetically build the hemoglobinopathies, the enzymopathies, and the cytoskeletal-membranopathies.

Unfortunately, this parasite-favouring cytoadhesion is part of what makes *P falciparum* so much deadlier to its host, compared with the other four malaria species which do not have this property. The mechanism by which the iRBC sticks preferentially to group A antigens has been deciphered, through the discovery of the lectin-like domain on the knob protein that redecorates the iRBC surface, courtesy of the new manufacturing directions of the parasite within. This domain, known as the Duffy-binding like domain (DBL1α), is part of the variable exon sequences of *Plasmodium falciparum* - Erythrocyte Membrane Protein 1 (PfEMP-1), which molecularly defines the adhesive pinnacle of the knobs. This is what binds all too well with the group A antigen, less so with B, and not at all with O.

EVIDENCE FOR ABO EFFECT, AND ITS NATURE, IN MALARIA		wild-type group A	mutant group O
CLINICAL:	**infectivity:** no	equal prevalence of infection	
	pathogenicity: yes	more severe disease	more uncomplicated disease
GEOGRAPHIC:	type distribution assocations with **endemicity:** yes	less prevalent in population	more prevalent in population
IN-VITRO:	**reverse-type activity** against *Plasmodial* sporozoites (which bear A-like antigens): no	n/a	anti-A: no appreciable innate parasitic clearance activity
	forward-type vulnerability to cytoadhesion with infected red blood cells (iRBC): yes 	more rosetting 	less rosetting 

This has potentially major implications. If we gain evidence for a major mortality difference for group O versus A, we shall be tempted to examine whether there is a role for type O over type-specific red cell transfusions for the management of severe malarial anemia, or perhaps even whole blood or therapeutic red cell exchanges for the management of severe syndromes of cytoadhesion such as cerebral malaria, wherein the blood flow to the brain itself is severely compromised by congestion. The results of the Cytoadhesion in Pediatric Malaria (CPM) Study, which recently finished enrolling over 2,000 children in Uganda in November 2009 (NCT 00707200, www.clinicaltrials.gov), are forthcoming. This is the first study to prospectively examine the differences in ABO (and certain other blood group) distributions between children who suffered with or succumbed to severe malaria, compared with those who only experienced uncomplicated malaria. If indeed patient ABO group proves to be as important as all the other evidence would suggest it to be, we may have an entirely new strategy to subdue this disease when antimalarial chemotherapies on their own are failing.

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Immunology for Dummies, Part 2: Immune Responses to Transfusion and Transplantation

The human immune system evolved to control infection by microorganisms. Bacteria are the most immediate threat and are destroyed by specific antibodies, whereas intracellular microorganisms and viruses are controlled predominantly by cytotoxic T cells. The huge number of polymorphic blood groups and human leucocyte antigens (HLA) in humans arose very recently in evolutionary terms, so the immune response to transfusion of human allogeneic cells or tissues utilises pathways designed for killing microorganisms.

The antibody response to bacteria or non-human red blood cells (RBC) takes about five days and always occurs because inflammatory signals from receptors recognising the foreign cells drive the immune response, with the aim of destroying the target cell. This mechanism may underlie naturally occurring anti-A and anti-B, possibly a cross-reactivity to bacterial sugars, see also page 16. In contrast, the antibody response to transfused ABO compatible allogeneic RBC is very slow (2-3 months) and of variable frequency. Why?

Antibody responses to transfusion

First, there are no receptors or recognition molecules for blood groups. In a sterile environment, there is nothing to alert the immune system to the non-self cells. This is fortunate, because it enables transfusions to be successful. Virtually all donor and recipient blood is mismatched for at least some of the blood group antigens that are not typed for. There is nothing to stimulate phagocytosis of the transfused RBC and they will circulate with a mean cell lifespan approaching 120 days. Then, the old red cells are recognised by splenic macrophages because they exhibit markers of apoptosis (programmed cell death) which trigger phagocytosis. This is non-inflammatory – it is happening all the time. For an antibody response to occur, the macrophage with internalised antigen must receive inflammatory signals (normally provided by microbial adjuvants) to mature into a dendritic cell and present antigen to T helper cells which in turn activate antigen-specific B cells to secrete antibody (see Part 1 in Issue 30). There will normally be very few inflammatory stimuli so an antibody response is not guaranteed.

However, the immune status of the recipient greatly affects the outcome. Three groups of patients illustrate this. Immunocompromised, old or immunodeficient RhD-negative patients may often not respond even to transfusion with RhD-positive blood. Pregnant women, however, can make robust alloantibody responses to small volumes of fetal blood acquired by feto-maternal haemorrhage (FMH). A mild systemic inflammatory state exists during pregnancy. Most blood groups were discovered by analysis of pregnancy-induced antibodies to RBC, platelets, neutrophils and lymphocytes (HLA). At the other end of the spectrum, sickle cell disease is characterised by severe inflammatory episodes and those patients who require many transfusions often develop multiple alloantibodies.

Antibody function

The consequences of antibodies are mainly a function of their isotypes. IgM antibodies (often to carbohydrate/sugar epitopes, e.g. anti-A, anti-B) stimulate RBC agglutination and complement-mediated haemolysis. Potentially fatal consequences of ABO incompatible transfusions are avoided by cross-matching. Protein antigens induce IgG1 and IgG3 antibodies, e.g. anti-D, that mediate phagocytosis of RBC through Fcγ receptors on splenic macrophages. With small doses of RBC, the cells are digested intracellularly, like apoptotic

cells, there is no haemolysis and it is non-inflammatory. This is the likely mechanism of action of prophylactic anti-D, when RhD-positive FMH are cleared "silently" by RhD-negative women. At large RBC doses, however, the phagocytic ability of splenic macrophages may be overwhelmed and RBC coated with anti-D are haemolysed extracellularly. This occurs in haemolytic disease of the fetus and newborn (HDN) when a RhD-positive fetus constantly receives high amounts of maternal anti-D by placental transfer. Also, rare fatal cases of acute haemoglobinemia or haemoglobinurea have been recorded in RhD-positive patients with immune thrombocytopenic purpura (ITP) following treatment with anti-D immunoglobulin.

Haemolysis is dangerous because of the toxicity and inflammatory activity of cellular components, including enzymes and haemoglobin, released from necrotic (killed) RBC. A cytokine storm or disseminated intravascular coagulation (DIC) may follow, leading to fluid overload (hydrops). Thus the same anti-D can be dangerous (HDN) or beneficial (prophylaxis) depending on the volume of target RhD-positive RBC.

Organ rejection

Rejection of solid organs is caused by recognition of donor HLA and minor histocompatibility molecules by the recipient. Therefore HLA matching of donor and recipient is important.

Hyperacute rejection of vascularised organs is due to the presence of preformed complement-fixing antibodies in the recipient that bind to donor endothelial cells causing thrombosis and ischaemia, within minutes. Cross-matching before grafting detects anti-HLA antibodies and also incompatible antibodies in the ABO blood group system.

Acute rejection within two weeks of transplant occurs after alloreactive responses to donor molecules develop. (a) The recipient's T cells may bind to donor HLA (± complexed with self peptides) on passenger macrophages, because it is conformationally similar to a foreign peptide-self HLA complex that T cells can recognise (direct presentation). (b) The recipient's macrophages may present donor peptides (after phagocytosis of transplanted cellular material) on their (self) HLA to their T cells (indirect presentation). Both types of responses result in recipient T cell activation and production of antibodies (as described in Part 1) or cytotoxic T cells (CTL) directed mainly towards endothelial cells, causing necrosis.

Antigen-specific CTL develop in stages. Macrophages present peptides from ingested donor material both on HLA class I molecules for presentation to CD8+ T cytotoxic lymphocytes and on HLA class II molecules for presentation to CD4+ T helper (Th) lymphocytes. Th cells help antigen-specific B cells to produce antibody and, with IL-2, also help antigen-specific CD8+ CTL to proliferate. Through their T cell receptor (TCRs), these alloantigen-specific CTL then recognise donor endothelial cells, stimulating cytotoxicity.

Acute rejection may be prevented by improved HLA matching and the use of drugs to reduce T cells, especially CD8+ CTL. Cyclosporine was introduced about 25 years ago and is still important; it blocks IL-2-dependent growth and differentiation of T cells. FK-506 (with a similar action), rapamycin (inhibition of T cell proliferation and reduction of antibody), mycophenolate mofetil (inhibitor of T cell differentiation), anti-CD3 (removal of T cells), azathioprine and cyclophosphamide (metabolic inhibitors of lymphocyte precursors) and corticosteroids (generalised anti-inflammatory activity, blockade of cytokine production by macrophages) are now included in the arsenal of anti-rejection agents. Long term use of immunosuppressive drugs to reduce CTL renders patients compromised in their ability to control viral infections such as CMV and malignancies caused by Epstein-Barr virus (B cell lymphoma). Avoiding necrosis in the organ before transplant, by reducing storage time and temperature, is very important because necrosis is inflammatory, leading to enhanced immune responses, tissue injury and immunogenicity.

Chronic rejection developing after several months is now the major cause of organ graft failure. IFN-γ secreted by alloreactive CTL and Th1 cells activates macrophages resulting in inflammation, necrosis and injury to blood vessel walls. Wound healing and mesenchymal growth factors secreted by the activated macrophages stimulates fibrosis and overgrowth of smooth muscle leading to arteriosclerosis (occlusion of arteries).

Graft versus host disease (GVHD)

Haematopoietic stem cell grafts are given to patients with leukaemia or compromised immune systems after ablating their bone marrow. Donor and recipient must be highly concordant for HLA. Donor CTL are necessary to prevent recurrence of leukaemia, but alloreactive donor CTL may also cause serious GVHD when donor cells attack the recipient. During acute GVHD, CTL recognise minor histocompatibility antigens causing necrosis of epithelial cells in the skin, liver and gut by activated macrophages and NK cells. Chronic GVHD is characterised by fibrosis of these organs. Strategies to prevent this potentially fatal outcome are removal of T cells from the graft (but with the risk of graft failure or losing the anti-leukemic effect) or infusing CD34+ stem cells and adding back T cells.

Future perspectives

Paradoxically, although pregnant women respond to fetal alloantigens, including HLA, the fetus is tolerated. Perhaps some of the natural mechanisms of immune tolerance during pregnancy could be harnessed to improve transplantation outcome?

Lecture slides on this topic may be viewed by Googling my name, accessing www.bbts.org.uk/PDFs/events/Immunology%20for%20Dummies.pdf

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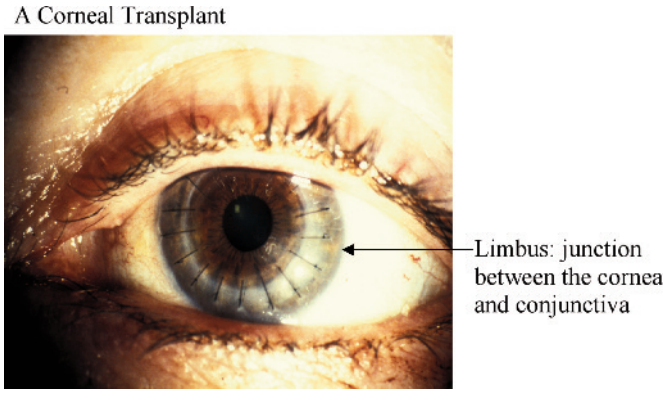
Transplantation of the Ocular Surface

At present the eye can contribute and can receive three types of ocular tissue for transplantation: cornea, limbus and sclera, and can also receive non-ocular amniotic membrane and autologous serum tears.

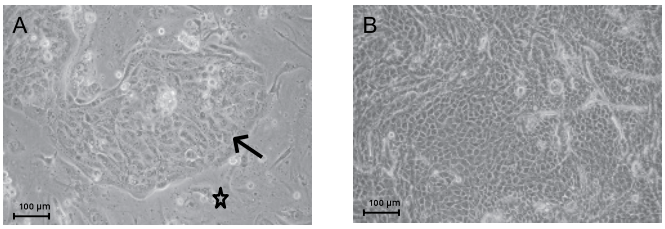
The ocular surface comprises the conjunctiva (an epithelial layer covering the sclera (white of the eye) and the inner surface of the eyelids) and cornea. The epithelium of the cornea is renewed by cells that migrate from the junctional zone between the cornea and conjunctiva, known as the limbus, which contains a population of corneal (limbal) stem cells. Corneal transplants become quickly populated with host corneal epithelium and it was the observation of the centripetal movement of corneal dots (epithelial cells) following corneal transplantation that led to the discovery of corneal epithelial stems cells at the limbus (figure 1).

Figure 1



Although corneal transplantation (Figure 1) is aimed primarily at restoring vision, unless the surface of the transplanted cornea can be maintained by regenerating epithelial stem cells, that corneal surface will ultimately fail. Thus, in cases where there is also limbal stem cell deficiency, these cells must also be replaced either autologously from the fellow eye, or as an allograft from a donor. It is now possible to expand the cells from a small piece of limbal tissue in the laboratory (Figure 2) for subsequent transplant. The ocular surface is also dependent on a healthy tear film and conjunctiva. Autologous serum tears are now in use, and research is underway to locate conjunctival stem cells so that they can also be expanded in vitro and transplanted to manage the many conditions which result in severe conjunctival scarring.

Figure 2



Phase contrast images of human limbal epithelial cells (arrow) expanded on 3T3 mouse fibroblasts(star) in tissue culture plates for A) 5 days and B) 14 days.

Autologous Serum Tears

None of the available artificial tear preparations include the essential growth factors required for the maintenance of a healthy ocular surface. One of the best substitutes and adjunctive to the tear film, comes from using a patients own blood as a source for autologous serum tears. This concept arose from the knowledge that serum is similar to natural tears in terms of pH, osmolarity and growth factors. There is a wealth of data from clinical trials showing the benefits of autologous serum tears in patients with ocular surface disease.

Amniotic Membrane Transplantation

Amniotic membrane (AM) is the innermost layer of the placenta. The epithelium of the AM rests on a basement membrane, which closely resembles that of the conjunctival basement membrane. Human AM is being increasingly used in the treatment of severe ocular surface diseases because of its ability to facilitate corneal re-epithelialization and reduce corneal scarring and inflammation. It is used extensively in corneal disorders such as ulceration, chemical injuries or in ocular surface reconstruction. More recently, it has been used as a substrate for cultured limbal stem cell transplantation.

Corneal Transplantation

The cornea is a delicate tissue and disease or injury may lead to a loss of transparency or a change in shape, resulting in severe visual impairment. For many patients, the only treatment option is corneal transplantation. This involves the removal and replacement of a circular disc of the patient's cornea with a similar disc of healthy tissue taken from a deceased donor's cornea. Approximately 3,000 corneal transplants are undertaken each year in the UK. It is a very successful procedure with over 80% survival of the graft at two years.

Progress in Corneal Transplantation

Traditionally corneal grafting has involved replacing all of the layers of the cornea (Figure 1). This technique known as penetrating keratoplasty often results in prolonged visual recovery of between 6-12 months. Over the past five years, there have been significant advances in the type of surgery offered for corneal transplantation, not only reducing the potential for rejection but also accelerating visual recovery.

Deep Anterior Lamellar Keratoplasty (DALK)

Keratoconus accounts for approximately 25% of corneal transplants. In this condition, the anterior layers of the cornea become thin so that the cornea bows forwards assuming a conical shape, hence the name 'keratoconus'. Equally, corneal scarring from infections often only affects the anterior layers of the cornea. These patients are usually young and have a healthy endothelium lining the back of the cornea. They may benefit from a new surgical procedure known as deep anterior lamellar keratoplasty in which only the anterior layers of the cornea are removed and transplanted, leaving the host endothelium intact. Not only is the risk of rejection reduced, but the integrity of the eye is less disturbed.

Endothelial Keratoplasty

The cornea (usually 0.5-1mm thick) can become 'water-logged' and thickened if the endothelial cells lining the back of the cornea fail, resulting in misty vision. This type of defect accounts for approximately 40% of corneal transplants. Surgical advances have led to transplanting only the endothelial layer, through a small incision, which leads to quicker visual recovery (usually a few weeks) and the eye is more structurally intact. Various names have been given to this procedure but the accepted term now used is Endothelial Keratoplasty.

Limbal Stem Cell Transplantation

Limbal stem cell deficiency (LSCD) occurs when there is significant damage to the limbus such that it is no longer able to support and maintain a healthy corneal epithelium. This leads to corneal desiccation, vascularisation and painful ulceration with loss of sight. A wide variety of conditions may lead to LSCD including: irradiation, chemical injuries, chronic contact lens wear and the chronic use of ocular medications. Treatment of corneal ulceration and scarring in these conditions by corneal transplantation alone is prone to failure because of the underlying LSCD. Restoration of the corneal epithelium is dependent on the presence of limbal stem cells and treatment now involves either direct replacement of the limbus from a healthy donor eye or by expanding a small sample of cells in culture (Figure 2) before transplantation. These techniques may be achieved either autologously from the fellow eye, or as an allograft from a donor.

Scleral Transplantation

Inflammation of the sclera may result in severe thinning and devices used in glaucoma surgery may erode through the conjunctiva. These threaten the integrity of the eye and can be managed with scleral patch grafts.

In summary, a variety of ocular transplants aid in the management of many diseases, and it has now become possible to selectively transplant different layers of the cornea. All of this however, depends on the generosity and altruism of the donors and their families.

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What has the HTA Achieved and What is its Future Mission?

Introduction

The Human Tissue Authority (HTA) has been regulating since 2006. As our fourth anniversary approaches this is a good opportunity to reflect on our achievements and to look to the future of both our organisation and the sectors we regulate.

The HTA has two key roles

Firstly, the licensing of establishments in the sectors we regulate: anatomy, post mortem, research, public display and human application. We now licence over 800 establishments and have conducted over 400 inspections.

Secondly, we play an important role in living donation, ensuring that living organ donors are fully aware of the risks associated with the procedure they are going to undertake and that they are not being put under pressure to donate. We must also check that the donor is not being offered a reward of any kind. Since 2006 we have approved over 3,000 living organ donations.

We fulfil many other roles, including offering advice and guidance to the sectors we regulate, as well as to the general public.

We work under two laws: the Human Tissue Act 2004 and the European Tissues and Cells Directive (2004/23/EC; 2006/17/EC; 2006/86/EC). Our aim is to make sure that these laws are followed by setting standards that are clear and reasonable, and in which the public and professionals can have confidence. Our work ensures that human tissue is used safely and ethically, with proper consent.

From the very beginning we have aimed to be a fair and balanced regulator, using a light touch approach but being willing to take regulatory action when required; and working in collaboration with a wide range of stakeholders.

Living Donation

The framework we established to fulfil our role in relation to living organ donation has been widely welcomed and supported by medical professionals. Initial concerns that this would create reams of extra paperwork and potentially delay donations were allayed early on and we continue to monitor and improve our systems.

We have 121 Independent Assessors (IAs); people trained by the HTA to conduct interviews with the potential donors and recipients in living donation, based across the UK. Our IAs work with Transplant Units to ensure the process works as smoothly as possible.

There has been a steady increase in the number of living organ donations since we started regulating in 2006/07 when there were 702 living transplants, compared with 1,026 in 2009/10. We are proud of the part we have played in increasing public confidence in living donation.

Much of the media coverage over recent years has focussed on altruistic and paired and pooled donations (see references) and the increasing number of people coming forward to donate in these ways. The fact that these types of donation have become accepted and celebrated is a significant move forward for living donation in the UK.

Cells and tissues used as a treatment

As the UK competent authority under the European Tissue and Cells Directive, the HTA licences and inspects those establishments that work with cells and tissues which will be used for human treatment.

We played a central role in interpreting and implementing this European legislation and contributed to the UK being one of the very first member states to incorporate it into domestic law (the Quality and Safety Regulations (Statutory Instruments 2006, No 1659 [37] and 1260 [38]). We licence over 270 establishments in this area who work on treatments for cancer and blood diseases such a leukaemia, as well as a host of other diseases and conditions.

Our regulation of this developing sector has helped secure the quality and safety of these treatments and in turn increase public awareness and confidence. In March this year we issued advice and guidance to parents considering cord blood banking and wrote to 150 organisations to warn them of concerns that unlawful umbilical cord blood collection may compromise safety and quality standards.

The Future

The Organ Donation Directive making its way through the European Parliament will undoubtedly have an impact on the transplant programmes in the UK and will be finished within two years commencing June 2010. The HTA worked with the Department of Health to ensure the Directive would work in practice.

The Directive will introduce increased levels of quality assurance and monitoring to organ donation and further increase public confidence in this area. The HTA have been heavily involved in the development of the UK's position on the Directive and we look forward to contributing further in the future.

The sectors we regulate continue to develop at a significant pace and we are already working on frameworks to consider face and uterine transplantation.

Rapid advances are being made in the use of stem cells as treatments so we are working closely with the establishments we licence to ensure we are up-to-date and able to provide advice and guidance in this area.

Our links with the transplant community allow us to keep abreast of the possible new forms of donation and we will work to facilitate these, while ensuring public confidence is maintained.

Across our remit we strive to engage, listen and communicate with the sectors we regulate and our experience of doing so over the past four years has been an extremely positive one. We aim to continue, and improve, on this approach in the future. Following the recent Arm's Length Body Review, it has been announced that our functions will eventually transfer to other organisations. Until then we are committed to carrying out our business as usual.

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REFERENCES

Website address for HTA Annual Report :-
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http://www.guardian.co.uk/society/2010/jun/16/living-donors-on-the-rise

The Extraordinary You Event

On an exceptionally rain swept Tuesday evening in February over 50 healthcare scientists made their way to 11 Downing Street for the formal launch of "Extraordinary You". Maggie Darling, wife of the then Chancellor of the Exchequer hosted the high profile event to celebrate the work of the scientists from a wide range of professions.

"Extraordinary You" is a project initiated by Professor Sue Hill to raise the profile of Healthcare Scientist careers and the variety of opportunities using science to improve the care of patients. Applications were sought from professions and organisations for scientists who epitomised the extraordinary work done. A group of approximately 100 scientists were chosen from within the NHS who represented the breadth of scientific expertise required to deliver the exceptional patient care and research of our health service. They were each interviewed by Vivienne Parry about the work they do and how their career has progressed. The interviews focused on how they felt about their work and why they chose to work within the NHS.

These interviews along with commissioned photographs were collated into a "coffee table" book entitled "Extraordinary You!". The aim of the book is to encourage people to choose science as a career and demonstrate the breadth of disciplines that it can be used in and how those disciplines directly affect patient care.

The professions represented included tissue banking, anatomical pathology, biochemistry, research etc. The reception provided a rare opportunity to mix with scientists of all levels and in an incredible number of professions.

There were a number of representatives from NHS Blood and Transplant at the reception. Rebecca Cardigan, Head of the Component Development Laboratory, Marion Scott, National Research and Development Manager and Helen Gillan, Head of Operations for Tissue Services all attended and enjoyed the event.

Professor David Anstee, Research Co-ordinator, Joyce Poole, IBGRL Red Cell Reference Manager and Kirstin Finning, Clinical Research Scientist at Filton, are also featured in the book.

The reception was introduced by Ann Keen MP, Health Minister who said "'Extraordinary You' gives healthcare scientists the recognition they deserve. The Prime Minister and the Government have rightly invested in science and research given its importance to advances in healthcare provision as well as to maintaining the UK's reputation as a world leader."

"As a nurse, I know about the amazing work that healthcare scientists carry out every day to improve the quality of patient care but it is usually nurses and doctors that attract the attention. I am so pleased that scientists have their rightful place on the front line."

"It is so important that we change conventional views of scientists locked away in hospital laboratories to one that is more current. More and more healthcare scientists are directly involved in the pathways of care for patients, regularly engaging face-to-face with patients as well as aiding doctors in up to 80 per cent of all clinical diagnoses."

Chief Scientific Officer, Professor Sue Hill then described the book and also the thinking behind it - "Healthcare scientists provide the most cutting-edge technology and science for patients in order to improve healthcare and 'Extraordinary You' profiles the vital research and patient care they provide."

"My work as a healthcare scientist for 20 years allowed me to carry out extremely rewarding work helping patients suffering from respiratory problems while, at the same time, carrying out research into longer term disease mechanism solutions to benefit patients in the future."

"I hope that the publication of 'Extraordinary You' will help patients, employers and commissioners recognise the work that they do and inspire others that a career in science in the NHS is an exciting and rewarding option."

The reception in Downing Street afforded the project the importance and weight that it deserved. The invitees were incredibly well looked after and were given a taste of life at Whitehall! The stories within the book are inspirational in terms of careers in science and I am sure that they will help to direct people into using their science to benefit patients.

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Transfusion Support in Stem Cell Transplant Patients

Haemopoietic Stem Cell Transplant (HSCT) patients are likely to require intensive blood component support. Careful selection of appropriate blood components is essential as these patients are profoundly immune suppressed and are at risk of transfusion associated complications, in particular:

- Haemolytic Transfusion reactions in ABO mismatched transplants
- Transfusion Transmitted Infections (TTI) – especially CMV
- Transfusion Associated – Graft Versus Host Disease (TA-GVHD)

They are, of course, susceptible to all the other complications of transfusion as reported to the SHOT scheme. In order to try and reduce these complications various measures are recommended. The 'triggers' for blood component support vary amongst units but generally red cell support is given when Hb <8g/L and platelet transfusion when platelets <10 x 10^9/L or <20 x 10^9/L if the patient has factors associated with increased platelet consumption e.g. sepsis. There is also increasing interest in the use of granulocyte transfusions for the secondary prevention and treatment of neutropenic sepsis.

ABO Mismatched Transplants

Approximately 15-25% of HLA matched sibling allografts differ in donor and recipient ABO blood groups and the figure is higher in alternative donor transplants. The ABO incompatibilities are defined as:

- Major ABO incompatibility - Recipient plasma has alloagglutinins that react with donor red cells e.g. Group A donor →Group O recipient.
- Minor ABO incompatibility - Donor plasma contains alloagglutinins that react with recipient red cells e.g. Group O donor →Group A recipient.
- Bidirectional incompatibility - Both recipient and donor plasma contain alloagglutinins reactive with donor and recipient cells respectively e.g. Group A donor →Group B recipient.

Allogeneic HSCT grafts contain donor red cells, lower numbers in peripheral blood stem cells - 3-5% of component value compared to 25 – 35% in bone marrow collections. In major compatibility this can lead to haemolytic transfusion reactions following transfusion of the haemopoietic stem cell components. These reactions can be reduced by therapeutic interventions in the recipient or processing of the Stem Cell Components if necessary. Haemolysis can also occur at 7-12 days post-transplant in the setting of minor ABO incompatibility when viable donor lymphocytes, ('passenger lymphocytes') in the graft are transfused as they are then restimulated to produce IgG anti A and B to recipient red cells antigens.

Post transplant manual crossmatching is required as the persistence of anti-donor alloagglutinins varies. Reduced Intensity Conditioning regimes are being used more in allografting and there are some reports to suggest there is an increased incidence of pure red cell aplasia but this appears to depend on the conditioning regime and the use of cyclosporin.

Transfusion Transmitted Infections

HSCT patients are at particular risk of CMV transmission if they are CMV negative and have a CMV negative donor. CMV status is tested for by serological testing as there is no evidence to suggest that PCR for viral DNA has a higher detection rate. In immunocompetent individuals acute CMV infection tends to cause a minor illness but the virus remains latent without clinical symptoms. The virus is transmitted in donor leucocytes present in blood components and replicates in the immunocompromised host to cause a serious, sometimes fatal, illness affecting lungs, eyes, gut and liver. HSCT patients are immunosuppressed from the high dose (chemotherapy +/- irradiation) conditioning therapy that they receive, as well as medication to prevent and treat graft versus host disease (GVHD) e.g. cyclosporin and steroids, and are therefore at risk of acquiring CMV infection from blood components. As the virus is transmitted in leucocytes there is some evidence that leucodepletion may be as effective as screening donors for serological CMV status to provide CMV seronegative products. However this strategy remains controversial and the current UKBTS recommendation is to provide CMV negative, leucodepleted blood components for those at risk.

Transfusion Associated Graft versus Host Disease (TA-GVHD)

TA-GVHD occurs when transfused alloreactive donor T-lymphocytes recognise recipient alloantigens, proliferate, produce cytokines and cause cell and tissue damage. In transfusion recipients with normal immune reactivity foreign HLA is recognised by recipient lymphocytes and the GVH response prevented. In HSCT patients this response is blunted and patients are susceptible to TA-GVHD which is a rare but fatal complication of transfusion with >90% mortality. Clinical features are fever, jaundice, rash, diarrhoea and pancytopenia. TA-GVHD can be prevented by gamma irradiation of all cellular blood components to inactivate lymphocytes; the minimum dose recommended is 25Gy to all parts of the component. Although leucodepletion if all blood components is done in the UK it is not considered adequate to prevent TA-GVHD. Since universal leucodepletion was introduced in the UK in 1999 there have been only three cases of TA-GVHD reported to SHOT and none since 2001.

Therapeutic Granulocyte Transfusions

Prolonged neutropenia can lead to severe bacterial or fungal infections in stem cell transplant patients. Initial studies did not show significant benefit from granulocyte transfusions but the yields were low. Currently there are two methods of obtaining adequate granulocyte doses: pooled buffy coats – recently developed by NHSBT as a pooled or optimised granulocyte component (PGC/OGC) or by apheresis collection from donors whose granulopoiesis has been stimulated with GCSF and steroids. It is recommended that granulocytes are irradiated to prevent GVHD. Well-designed prospective studies are required to provide evidence on the therapeutic benefit of granulocyte transfusions, the toxicities, dosing and the feasibility of harvesting from donors. Granulocyte donors must be ABO and ideally CMV compatible.

Summary

HSCT patients are very immuno-compromised and susceptible to all the complications of transfusion. Appropriate selection of blood components is important to reduce complications in stem cell transplant patients. Particular challenges include changing ABO blood groups, the prevention and management of infection and the need for irradiated blood components. All hospitals that provide blood components to HSCT patients should have clear policies and procedures; regular audit of transfusion outcome is recommended. BCSH recommend all blood components for susceptible patients are irradiated and CMV negative products provided for patients at risk.

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Review of the 'Red Book' Organisation and Plans for the Future

Moves to develop commonality in transfusion practices and standards between the four UK Blood Services began in 1987 when the forerunner of what is now known as the Joint Professional Advisory Committee (JPAC) was set up. Guidelines for the Blood Transfusion Services in the United Kingdom, which later became known as the "Red Book" guidelines, were first published by this group in 1990. The Red Book is now in its 7th edition with the 8th edition planned for the end of 2010.

JPAC has a dual remit, which is to prepare detailed service guidelines for, and to be an Advisory Committee to, the UK Blood Services. The Committee reports to the Medical Directors of the individual services, who are themselves accountable to the Chief Executives. The Medical Directors and Chief Executives collectively combine as a group known as the UK Forum. Further information on JPAC, including its current structure, can be found on www.transfusionguidelines.org.uk

Since JPAC was first set up there have been many changes in transfusion practice and management both in the UK and internationally. In particular, the EU Directive on Blood (and subsequent translation of this into the Blood Safety and Quality Regulations) in 2005 set out new legal standards and requirements. The independent Advisory Committee on Safety of Blood Tissues and Organs (SaBTO) was set up in 2008, with the objective of making high level recommendations to Ministers on the safety of blood, tissues and organs for the UK. Guidelines for transfusion services, particularly around some aspects of blood safety, were increasingly being made independently of the UK Blood Services, which inevitably led to questions about the continuing relevance and role of JPAC and the Red Book. In addition, with pressure on the cost of public services and increasing difficulty in recruiting experienced staff, it is ever more essential that scarce resources are utilised in the most effective manner possible and duplication of effort is avoided. In view of the legislative changes and a desire to ensure that resources were being properly utilised, the UK Forum commissioned a review of JPAC in 2009.

The scope of the review was twofold – firstly to review all of JPAC's current activities and define the primary purpose and objectives of JPAC (including whether its existence was still appropriate), and secondly to review JPAC's modus operandi and how best it can achieve those revised objectives. The review was conducted primarily by interviews between Consultants and a variety of stakeholders with an interest in the JPAC organisation, including Blood Services, Health Departments, JPAC members, the MHRA, and Chairs of organisations external to the Blood Services e.g. SaBTO, National Blood Transfusion Committees, and the National Patient Safety Agency.

There were several common themes which emerged from the interviews. Firstly, it was gratifying to note that JPAC was "highly valued", particularly the Red Book and Handbook of Transfusion Medicine, and interviewees felt that the organisation presented a unified coherent voice for the four UK Blood Services. There was no support for disbanding JPAC.

However, there was a strong feeling that JPAC needed to increase clarity about the roles and remits of JPAC and its committees, and the representation of those serving, and provide greater transparency about the essential relationships with other committees and agencies in the UK blood community. There was also a feeling that although within the JPAC organisation communication was good, external communication to others not directly involved with work in the JPAC committees could be improved.

It was considered that the central function of JPAC as a hub of professional advice and guidance was not duplicated elsewhere, but some of the Standing Advisory Committee (SAC) work may be duplicated in other Blood Service and external committees.

There was a consensus that JPAC was effective, especially in delivering guidelines and updates. It was, however, noted that the SACs frequently relied on work being done on a "grace and favour basis" where the members did not have time specifically defined in their work plans for JPAC activities, which has the potential to reduce effectiveness. It was felt that there could be clearer accountability and governance procedures.

The review has provided reassurance that JPAC continues to be an important and central part of the UK Blood Services' advisory machinery. The conclusion is that the purpose of JPAC, as outlined above, will be unchanged, but that efficiency could be improved. Some aspects of the operation of the SACs will be streamlined and strengthened. Central to this will be a JPAC business plan which will be developed in conjunction with SAC work plans and the requirements of the UK Forum. In this way, JPAC can ensure that its agenda can be set with both a scientific focus provided by experts in the field, and the business requirements of the UK Blood Services, in mind.

Other specific areas identified by the review for further action are as follows:

- Review Terms of Reference and membership of SACs to ensure fit for purpose and clear roles. We will investigate whether main committees may be able to have a smaller core membership, but with additional experts and members co-opted for specific "task and finish" groups to be convened for specific projects.

Getting the support of employers of committee members is vital to the efficient operation of the SACs.

- Review timing and mode of committee meetings with flexibility of working encouraged to ensure that SACs deliver work schedule effectively.
- Monitor outputs of JPAC in a more structured way, e.g. completion of SAC work plans, reviewing timeliness of issue of change notifications, get feedback on outputs which go out to the wider Transfusion Committee, e.g. the Red Book and Handbook of Transfusion Medicine.
- Review JPAC policies to improve governance e.g. selection and turnover of Chairs and members of SACs, accountability and indemnity, decision making framework to ensure that it is evidence based and documented.

Communication with external organisations was seen as an important area for improvement. Communication routes will be revised, identifying the most influential stakeholders and ensuring that communication routes with them are optimal.

Lastly, although the JPAC website was not included in this review, it is recognised that the website is critical to JPAC output and communication. A Website Manager will be appointed to replace Dr Six following his sad death last year, and a review of the website will follow to ensure that it is fit to support JPAC going into the future.

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Next Edition

Issue 32 will feature articles on:

- Blood Provision for Difficult Patients
- BCSH Administration of Blood and Blood Components
- Historical Perspective of Blood Transfusion in War-Time Britain
- Component Development in NHSBT
- Cell Therapy for Articular Cartilage Repair: Past, Present and Future
- A Day in the Life of a Scientist in a Regional Burns Centre
- Knowledge is Power

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

CPD Questions

1. Thromboelastography in Practice:

A. Thromboelastography is a new test of functional haemostasis performed on whole blood.

B. Thromboelastography does not assess the contribution of cell surface interactions.

C. Thromboelastography assesses the kinetics of a forming clot.

D. Thromboelastography is not affected by platelet activation during blood sampling.

2. Pathogen Reduction Technologies

Platelets can be treated with amotosalen and ultraviolet light or riboflavin and ultraviolet light:

A. The process does not damage the therapeutic product.

B. The parent compound of amotosalen is toxic.

C. Mitochondria in platelets are not damaged.

D. Membranes of cells do not absorb the photo-energy.

3. Pathogen Reduction Technologies:

A. Current technologies are particularly effective against non-enveloped viruses.

B. Pathogen kill of current technologies is limitless.

C. Pathogen reduction will end all virology testing of donors.

D. Pathogen kill of current technologies is in the order of 10^6 for most enveloped viruses.

4. SaBTO

Risk Reduction Measures for vCJD:

A. Recommendations are made on risk reduction alone.

B. Will include universal importation of Red Cells.

C. Only applies to those born after 1st January 1996.

D. Includes a recommendation on importation of FFP.

5. Current Topics under review, do not include:

A. Use of ABO 'mismatched' Platelets.

B. Consent for Blood Transfusion.

C. Processing of femoral heads used in hip revision surgery.

D. Use of cryoprecipitate.

6. Enhancing Patient Care – Framework for Safe Blood Transfusion Practice

Section 130, 1968 Medicines Act as amended by regulation 25 of the Blood Safety and Quality Regulation 2005:

A. Excludes whole human blood and blood components from a legal definition of a medicinal product.

B. Requires a Registered Medical Practitioner to prescribe blood components.

C. Requires a Transfusion Medicine Consultant to prescribe blood components.

D. Includes whole human blood and blood components as a legally defined medicinal product.

7. Developing an Online Blood Ordering System (OBOS):

A. OBOS not required due to excellent fax quality.

B. OBOS not required as manual transcription errors do not occur.

C. OBOS has not yet been piloted.

D. OBOS will be implemented during 2010.

8. Landsteiner Meets Haldane:

A. Group O is the most ancient wild-type of the ABO system.

B. Group A Red Cells rosette best with infected Red Cells.

C. Group O Red Cells protect against malaria infection.

D. Pathogenicity is not affected by ABO type.

9. Immunology for Dummies:

A. The antibody response to bacteria is very slow (2-3 Months).

B. Inflammatory signals from receptors recognising the foreign cells slow the immune response.

C. Naturally occurring Anti-A and Anti-B are possibly due to a cross-reactivity to bacterial sugars.

D. Human leucocyte antigens in humans arose very early in evolutionary terms.

10. Immunology for Dummies:

A. Receptors exist for molecules of blood groups.

B. Patients with sickle cell disease characterised by severe inflammatory episodes rarely develop alloantibodies.

C. IgM antibodies are often to protein antigens.

D. An antibody response occurs if macrophages with internalised antigen receive inflammatory signals to mature.

11. Transplantation of the Ocular Surface:

A. The only ocular tissues that can be used in transplantations is the cornea.

B. Non-ocular tissues cannot be used in ocular treatments.

C. Limbal stem cells can be expanded in the laboratory.

D. Artificial tear preparations include the essential growth factors for the maintenance of a healthy ocular surface.

12. Transplantation of the Ocular Surface:

A. Amniotic membrane transplantation facilitates corneal re-epithelialisation.

B. Amniotic membrane is the outermost layer of the placenta.

C. Corneal transplant has a poor success rate of less than 40% survival at two years.

D. Autologous serum tears have little benefit in ocular surface disease.

13. Transplantation of the Ocular Surface:

A. Endothelial Keratoplasty accounts for approximately 40% of corneal transplant.

B. Keratoconus accounts for most of corneal transplant.

C. Inflammation or thinning of the sclera are not amenable to treatment.

D. Keratoconus due to corneal scarring from infections only affect the elderly.

14. HTA

Licensing does not include the following sector:

A. Anatomy.

B. Post Mortem.

C. Blood Transfusion.

D. Public Display.

15. Transfusion Support in Stem Cell Transplant Patients:

A. Approximately 15-25% of HLA matched sibling allografts differ in donor and recipient ABO blood groups.

B. Minor ABO incompatibility example Group O recipient, Group A donor.

C. Major ABO incompatibility example Group A recipient, Group O donor.

D. 'Passenger lymphocytes' do not cause a problem in the setting of a minor ABO incompatibility.

Diary Dates

2010

2-5 September 2010

1st World Congress on Controversies in Hematology (COHEM).

Location: Rome, Italy

For more information contact Enquiries on: lana@comtecmed.com

You can view the programme and register online: **http://www.comtecmed.com/cohem**

Details:

Chaired by Prof. G. Saglio and Prof. E. Rachmilewitz, the 1st COHEM Congress is based on a unique concept of discussion and interactive participation regarding controversial issues facing clinicians in 2010.

2-3 September 2010

2nd National Conference: Haematological Malignancies.

Location: Institute of Physics, London

For more information contact Dr Lisa Freeman on +44 (0) 207 501 6768 or lisa.freeman@yahoo.co.uk

You can view the programme and register online: **http://www.mahealthcareevents.co.uk**

Details:

This major two-day conference is designed to provide an update in the advances in diagnosis and treatment of the main haematological malignancies, and will prove indispensable for haematologists, clinical and paediatric oncologists, and transplantation specialists, as well as specialist nurses and trainees.

6-7 September 2010

The 2nd International Symposium on Critical Bleeding.

Location: Moltkes Palace, Copenhagen, Denmark

For more information contact: **www.ISCB2010.dk**

8-9 September 2010

UK NEQAS for Blood Coagulation Annual Scientific Meeting.

Location: The Atrium, Sheffield Hallam University, Sheffield

For more information contact Timothy A L Woods on +44 (0)114 267 3305 or Tim.Woods@coageqa.org.uk

You can view the programme and register online: **http://www.ukneqasbc.org**

9-11 September 2010

BBTS 28th Annual Scientific Meeting Bournemouth 2010.

Location: Bournemouth International Centre, Bournemouth

For more information contact Cath Riley on +44 (0)161 232 7999 or events@bbts.org.uk

You can view the programme and register online: **http://www.eventsforce.net/asm10**

Details:

The 28th BBTS Annual Conference will return to Bournemouth with the commitment to maintaining the highest standard of scientific education including our very popular Special Interest Group day and award lectures.

15 September/16 September/25 November 2010

Current Treatment Options in Haematological Malignancy & Support.

Location: The Lighthouse of Glasgow, Glasgow

For more information, contact: **http://www.hartleytaylor.co.uk**

16-17 September 2010

University Hospital of North Staffordshire Haematopathology Course.

Location: Staffordshire University, Stoke On Trent, Staffordshire

For more information contact Ms Nichola Grey - Course Coordinator/Senior BMS Morphology on +44 (0)1782 554622 or Nichola.Grey@uhns.nhs.uk

Details:

This course, which includes both lectures and work at individual microscopes, is suitable for staff grade haematologists and advanced trainees in haematology. It is also ideally suited to Specialist Registrars in Haematology and Histopathology preparing for the Royal College exams.

20-24 September 2010

Manchester Blood Coagulation Course.

Location: Manchester

For more information contact Jan Dixon on jan.dixon@uhsm.nhs.uk

Details:

This well-established course is intended to prepare candidates for the Royal College of Pathologists examination in blood coagulation. It is held in city centre Manchester at the Manchester Cathedral Visitor Centre.

20-22 September 2010

Haematology in Obstetrics.

Location: University of Leicester

For more information contact Julie Woolley on 0116 258 6534 or julie.d.woolley@uhl-tr.nhs.uk

Details:

This is a multidisciplinary course suitable for consultants, trainees and specialist nurses and midwives. The aim is to develop the skills and competencies of health professionals in managing haematological issues in pregnancy. It includes didactic teaching on major topics together with interactive sessions and workshops.

27 September 2010

Acute Leukaemia Day.

Location: IET Birmingham, Austin Court, Birmingham

For more information contact Dominique Calton on 01844 275650 or dom@hartleytaylor.co.uk

You can view the programme and register online: http://www.hartleytaylor.co.uk/

27 September - 1 October 2010

42nd Advances in Haematology Course 2010.

Location: Imperial College London, Hammersmith Campus, London

For more information contact A Sale on a.sale@imperial.ac.uk

You can view the programme and register online: http://www.w12conferences.co.uk

Details:

This course provides an intensive update on the scientific basis and clinical practice of haematology for haematology specialists and those in haematology training. The entire breadth of haematology is covered over five days, with emphasis on recent advances and their impact on future research or clinical management.

29 September - 1 October 2010

21st Annual Conference: British Society for Histocompatibility and Immunogenetics.

Location: The Royal College of Physicians of Edinburgh

For more information contact: www.bshi2010.org.uk

7 October 2010

Induced Pluripotent Stem Cells: Production and Utility in Regenerative Medicine.

Location: BioPark Hertfordshire, Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AX, UK.

For more information contact Astrid Englezou on 08714 890 134 or enquiries@euroscicon.com

You can view the programme and register online: http://www.regonline.co.uk/IPS09

8 October 2010

Discussion Workshop: Improving Immunohistochemistry 2010.

Location: The Biopark, Herts

For more information contact Enquiries on enquiries@euroscicon.com

You can view the programme and register online: http://www.regonline.co.uk/workihc2010

Details:

This event is an advanced workshop. We have invited six experts to discuss their work in an informal lecture setting, discussion and demonstration groups, one-to-one sessions and panel discussions. This event has CPD accreditation. On registration please submit your questions to the panel that will be asked by the Chair on the day of the event.

9-12 October 2010

AABB – Annual Meeting & CTTXPO.

Location: Baltimore, Maryland, USA

For more information contact: www.aabb.org.

10-13 October 2010

XXXII World Congress of the International Society of Hematology.

Location: Jerusalem, Israel

For more information contact ISH 2010 on ish2010@kenes.com

You can view the programme and register online: **http://www.kenes.com/ISH2010**

Details:

ISH 2010 provides an essential platform for hematologists from around the world to discuss problems with colleagues and experts and to discover the latest research, therapies and tools available in this constantly evolving field. This advanced world congress features a state-of-the-art scientific program that furthers the aims of the International Society of Hematology (ISH).

18-19 November 2010

Transfusion Tomorrow.

Location: The Royal College of Pathologists, London

For more information contact: **http://www.rcpath.org/conferences**.

4-7 December 2010

American Society of Hematology (ASH) 52nd Annual Meeting.

Location: Orange County Convention Center, Orlando, Florida, USA

For more information please contact Graz Fontanini on +44 20 7962 9030 or graz@lotusgroup.co.uk

You can view the programme and register online: **http://www.lotusconferences.com**

6-10 December 2010

BSI Congress 2010.

Location: Arena & Convention Centre, Liverpool

For more information contact: **www.immunology.org/congress2010**

2011

27-29 January 2011

T-cell Lymphoma Forum 2011.

Location: Hotel Nikko, San Francisco, CA

For more information contact Damaris Cruz on 201-594-0400 or dcruz@jwoodassoc.com

You can view the programme and register online: **http://www.tclf2011.com**

Details:

This forum will provide a platform for discussion about the classification, epidemiology, prognosis, and pathogenesis of several T-cell lymphoma subtypes. In addition, the latest information on novel agents and treatment approaches will be presented by T-cell lymphoma experts. This meeting is intended for haematologists, oncologists, and other clinicians and scientists with an interest in T-cell lymphoma.

10 March 2011

Identifying T Cell Subset Phenotype and Function in Infections.

Location: BioPark Hertfordshire, Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AX, UK

For more information contact: Astrid Englezou tel: 08714 890 134 or via email enquiries@euroscicon.com

The programme can be viewed and to register online go to: **http:/www.regonline.co.uk/tparasite09**

11-15 April 2011

Manchester Blood Coagulation Course.

Location: Manchester

For more information contact Jan Dixon on jan.dixon@uhsm.nhs.uk

Details:

This well-established course is intended to prepare candidates for the Royal College of Pathologists examination in blood coagulation. It is held in city centre Manchester at the Manchester Cathedral Visitor Centre.

A full diary of events and training courses can be viewed on the following websites:

www.transfusionguidelines.org.uk
www.blood.co.uk/hospitals
www.bbts.org.uk

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