

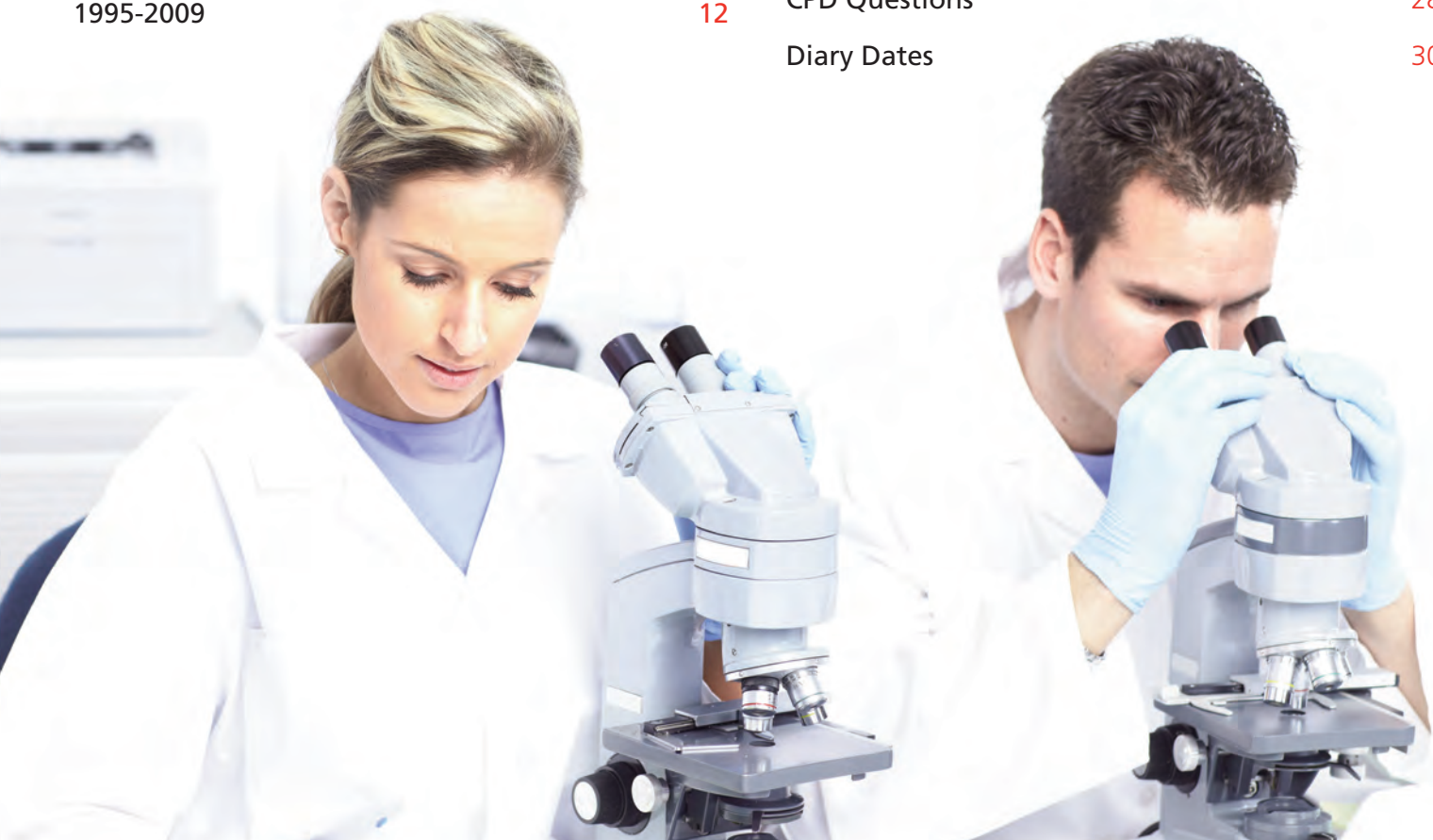
# Blood and Transplant

Information for hospitals served  
by NHS Blood and Transplant

# Matters

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# EDITORIAL

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The pace of change within the field of blood transfusion continues relentlessly, some of it scientific and some organisational. Frequently one stands back to survey an organisation like NHS Blood and Transplant, feeling that surely we must be about to level off, that no significant changes are needed for another few years, only to find that major developments are impacting in several areas. *Blood and Transplant Matters* tries to embrace as many of these developments as possible in its pages, in addition to publishing articles of a general educational nature.

As always I hope that we have achieved a good balance in our contents and trust that you will agree. Articles are divided loosely into those dealing with clinical blood transfusion practice, research and audit, tissues stem cells and organs and special articles such as 'a day in the life of', pioneers in transfusion and transplantation and so on. I am not going to reiterate the contents page here – you can read it for yourselves. The feedback that we receive from our readers is usually very positive and sometimes includes offers to write for *Blood and Transplant Matters* which we are always pleased to consider. All articles that we publish are peer-reviewed by the Editorial Board and in some cases we ask additional experts for their views, always aiming for high quality contributions. We do make mistakes, a sign that we are just like everyone else and you will see that we have included an errata section in this issue.

Derek Norfolk will have retired by the time that you read this and I am grateful to him for his invaluable support during my tenure as Editor. He has been on the Editorial Board for five years and I would like to wish him a long and happy retirement. Derek kindly reads these Editorials before they go to press and I hope that he will have cast his eyes over this one before he hangs up his stethoscope.

We plan to start including short, state-of-the-art research summary pieces in future editions, they will be hot off the press so as to include the most up-to-date information. Other plans include articles on transfusion in developing countries and more articles in our 'Immunology for Dummies' and 'Clotting for Idiots' series.

I sometimes wonder if progress is always a good thing. We seem to be like sharks, feeling that unless we move forward we die. Bertrand Russell articulated the alternative viewpoint when he said that: "The process which led from the amoeba to man appeared to be progress to the philosophers, although whether the amoeba would agree with this opinion is not known." That said, our mission is to save and improve lives and as long as that is the focus of our activity then we are on the right track.

That great time traveller Arthur C Clarke stated that: "Anything that is theoretically possible will be achieved in practice, no matter what the technical difficulties are, if it is desired greatly enough." Well he didn't have to cope with a recession, spending cuts and miles of red tape but I feel sure that he would have found a way through it all! So common purpose and a shared sense that what we do is best for our patients is crucial.

Happy reading. If you like what we do, please let me or my indefatigable Editorial Assistant Carol Griffin know; if you don't please word it tactfully!

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## Hospital Blood Transfusion Training Passport – Experiences from the West Midlands Region

The Serious Hazards of Transfusion (SHOT) scheme has highlighted over the years that robust education and training in blood transfusion is vital to improve patient safety. The National Patient Safety Agency (NPSA) stipulates three yearly competency assessments of all hospital staff involved in the blood transfusion process for the activities they are involved in (blood sampling, collection of blood components and delivery to the clinical area and blood administration). The British Committee for Standards in Haematology (BCSH) recommends at least one update training episode in-between the three yearly NPSA required competency assessments (thus an individual receives training and/or competency assessment at least every two years). The Health Service Circular 2007/001 Better Blood Transfusion, Safe and Appropriate use of Blood advocates regular documented transfusion training and the NPSA's competency assessment requirements.

It has been recognised that many hospitals struggle to maintain these training and competency assessment requirements, and this is exacerbated by staff moving to new jobs in different hospitals.

Historically, when members of staff move from one organisation to another, all mandatory training has to be repeated, but there are many aspects of mandatory training that are 'passportable'. For example, when looking at fire training, the theoretical background knowledge of how fires start is the same regardless of where an individual works. What is of vital importance to new starters are the practical elements of fire safety and management in their new environment. If this theoretical aspect of the training is 'passportable', then on induction to a new organisation, the training given can be more practical and specific to the organisation, job role, environment and patient/client group.

### **The West Midlands Mandatory Training Passport**

In 2009, Education Leads from across the NHS West Midlands identified the need to standardise core aspects of Mandatory Training, with four main objectives:

- Support organisations to achieve national standards
- Ensure a consistent level of training across the region
- Increase the amount of time staff spend in service
- Enable organisations to utilise training time and funds more effectively.

A training passport was developed in partnership between NHS West Midlands and NHS London and in

collaboration with NHS South Central and Cheshire and Merseyside Primary Care Teaching Trust, with an ultimate vision of national standardisation of mandatory training. Intense work has been carried out to ensure that the passport scheme supports National Quality Assurance standards.

Figure 1 shows the current content of the training passport. Hospitals can sign up to either all, or specific sections of the passport.

#### **Figure 1: Current Content of the West Midlands Mandatory Training Passport**

- Conflict Resolution
- Conflict Resolution (Mental Health)
- Conflict Resolution Refresher Training
- Equality and Diversity
- Fire Safety
- Health, Safety and Security
- Infection Control and Prevention
- Moving and Handling
- Blood and Blood Components
- Resuscitation
- Safe Guarding Children
- Safe Guarding Vulnerable Adults

Each section of the passport has specified learning outcomes. Participating hospitals must agree to incorporate and embed the identified learning outcomes into the training delivered within their organisation. These learning outcomes are the minimum requirements and organisations are allowed to add additional learning outcomes to meet local policy requirements.

Hospitals also need to ensure that training is recorded in a way that allows the training records to be transferable between organisations. This can be done either electronically using the Oracle Learning Management system (OLM) within the Electric Staff Record (ESR), or where organisations are not using this system; a paper based method has been developed.

The first initial phase of the training passport went live in the West Midlands region in 2010 with most Acute Trusts (as well as many other primary health care organisations) signed up to participate.

## Blood Transfusion Training

The blood transfusion section of the passport went live in the second phase during Spring 2011. This was following in-depth consultation with the West Midlands Regional Transfusion Committee and the West Midlands Transfusion Practitioner group.

It was agreed that the blood transfusion section needed to be sub-divided into the various elements of the clinical blood transfusion process (ie blood sampling, blood collection, blood administration and appropriate use of blood components) so that individuals only need to complete training for the activities they are involved in.

Each of these sub-sections has the minimum learning outcomes specified (see example in figure 2). These reflect the learning outcomes from the nationally recognised *learnbloodtransfusion* e-learning course, and should be included in the minimum training for all staff involved in those activities, in both initial and refresher training, according to organisational policy. The mode of delivering the training has not been stipulated, and a variety of techniques may be employed to meet the learning outcomes, not just face-to-face training (eg e-learning). Frequency of blood transfusion training was also not specified, as apart from the guidance offered by the BCSH there is no clear national recommendation or requirement. Each organisation should perform a local training needs analysis to identify these minimum training requirements.

### Figure 2: Blood Sampling Learning Outcomes

- Identify the most common errors and risks in the blood sampling process, as described by the Serious Hazards of Transfusion (SHOT) scheme ([www.shotuk.org](http://www.shotuk.org))
- Demonstrate an understanding of the importance of blood group systems in the provision of compatible blood
- Ensure that the blood request form is completed clearly and accurately
- Explain the importance of meticulous checking of the patient identification details
- Explain how to correctly undertake the formal positive patient identity check and explain the importance of correctly labelling the blood sample next to the patient
- Describe how to communicate effectively with the hospital transfusion laboratory to ensure that the right patient receives the right blood at the right time.

## Blood Transfusion Competency Assessment

In the initial stages of developing the blood transfusion section of the passport, it was envisaged that the NPSA Blood Transfusion Competency Assessments would also be included. However, after in-depth discussion and analysis, it was agreed that this was not practical.

The NPSA competency assessments had been developed with the key aim of reducing wrong blood incidents due to patient misidentification. However, the actual competency assessment frameworks are much more in-depth and include all of the practical aspects of the processes involved. Therefore, although these national competency assessment frameworks are used by each organisation, individuals are assessed to local hospital policies and procedures and, for example, the use of different technologies. Therefore, organisations would need to complete a gap analysis for each individual to determine what elements of each competency needed to be re-assessed. Apart from this being a very time consuming exercise, it was identified that a gap analysis may indicate that the only aspect of the competency assessment that could be passported was that of positive patient identification, resulting in this vital process being seen as a less important part of the procedure. It was therefore agreed that competency assessments must be completed at local level and have not been included in the passport.

## Conclusion

Robust education and training in transfusion is vital to improve patient safety. When individuals move from one organisation to another, it is important that they are made aware of the differences in the procedures between the hospital they have just left and the new hospital. In order to allow organisations to concentrate on these important practical aspects, and to ensure a consistent level of training across the region, the West Midlands Mandatory Training Passport has been developed.

Uptake of this training passport scheme in the West Midlands region has been high, with more than 80% of Acute Trusts currently committed. Use of the scheme will be audited and changes can be made depending on the audit results and feedback received.

Although blood transfusion competency assessments have not been included in this passport, it is hoped that the inclusion of blood transfusion training will not only help organisations to deliver practical safe transfusion training to new members of staff, but also that this will help to standardise the training given.

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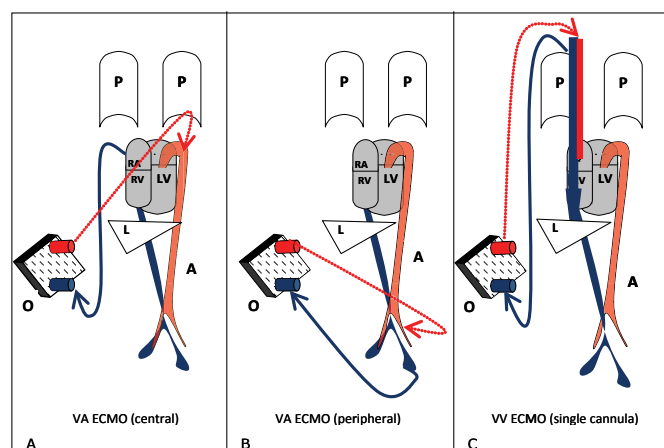
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## The Rise of Extracorporeal Membrane Oxygenation (ECMO) and Implications for NHS Blood and Transplant

Extracorporeal membrane oxygenation (ECMO) has received a lot of media and scientific attention in the past two years due to the H1N1/2009 flu pandemic and the high number of young patients with adult respiratory distress syndrome that benefited from it.

A membrane oxygenator combined with a pump and large bore cannulae access allows extracorporeal gas exchange to take place outside the body (see Figure 1). In addition, the pump used in the ECMO circuit can support the whole heart in some configuration (veno-arterial (VA) ECMO).

**Figure 1**



VA ECMO (A,B) allows replacement of heart function in addition to extracorporeal oxygenation. In central VA ECMO (diagram A) oxygenated blood is returned to the Aorta while in peripheral VA ECMO oxygenated blood is returned to the femoral artery.

VV ECMO (C) returns oxygenated blood into the venous system. C depicts the one cannula technique.

P: Lung, RA: right atrium, RV: Right Ventricle, LV: Left Ventricle, L: Liver, O: Oxygenator, A: Aorta

Diagram courtesy of Dr. Guillermo Martinez, Papworth Hospital, UK

The first successful report of ECMO for adult respiratory distress syndrome was published in 1972 but randomised controlled trials conducted subsequently failed to show a significant survival benefit of veno-venous ECMO until the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial published in 2010. This trial was conducted from July 2001 to August 2006 and seventy UK centres participated. Patients with severe respiratory distress were randomised to receive either conventional therapy or to transfer to a specialised centre (Glenfield Hospital, Leicester) where ECMO or best conventional therapy was performed. One hundred and eighty adults were included and the trial recruited patients with potentially reversible respiratory failure aged between 18-65 years. 68 (75%) patients actually received ECMO, 63% (57/90) of patients allocated to ECMO survived to six months without disability compared to 47% (41/87) of those allocated to conventional management. This trial demonstrated that transfer to a specialised centre that can offer ECMO if indicated, is a successful treatment strategy. This was subsequently reinforced by Moronke et al who showed that patients with H1N1 who had received ECMO had better survival than identical patients who were

not offered the treatment. Emerging evidence strongly suggests that ECMO is a reasonable strategy to support lung recovery in cases of Acute Lung Injury.

ECMO can be used to support both cardiac and respiratory function, and the success of this approach is still debated. It is likely that with the advent of new materials and therapeutic options that this treatment strategy will be used more often in the management of acute cardiogenic shock. In these cases, ECMO is used as a bridge to recovery or another treatment, such as mechanical assist devices. ECMO might also be useful in enhancing the benefit of cardiopulmonary resuscitation.

In all its modalities, ECMO has a substantial impact on the haematology resources of the hospitals that provide this service. Blood components, particularly von Willebrand Factor and platelets are subjected to highly unusual flow patterns during ECMO. The rapid aspiration and reinjection of blood through the cannulae leads to relative depletion of High Molecular Weight Multimers of von Willebrand Factor. The rapid flow of platelets through centrifugal pumps and heparin coated tubing systems is followed by a slow trickle through the oxygenator device with long dwell times. These activated platelets are sequestered within the perfusion system and by liver and spleen upon return to the patient's circulation. There is a degree of contact factor activation and patients are routinely put on full dose unfractionated heparin with augmented Partial Thromboplastin Time Ratios (APR) between 1.7 and 2.8.

Haemorrhage is a major and frequent complication. Intracranial bleed or nasopharyngeal haemorrhage are both life-threatening problems and sadly occur regularly in these patients. Treatment of these complications is difficult as the patient is at risk of thrombosis and embolism. Coagulopathy due to other causes, eg disseminated intravascular coagulation (DIC) or hepatic impairment, have to be considered.

In our institution, it is routine practice to provide the clinical areas with two to four units of compatible packed red cells available at all times, even in the most stable patient. Any complication can lead to catastrophic haemorrhage. For that purpose, platelet counts are usually maintained  $>100 \times 10^9/L$ .

This has logistical implications for the hospital transfusion laboratory to ensure the serological validity of the cross match sample in these multiply transfused patients and the need to provide platelets quickly in such a scenario. Furthermore, frequent red cell transfusions increase the risk of HLA sensitisation and poor platelet increments.

Where bleeding complications arise, the current expert consensus is to maintain the platelet count greater than  $150 \times 10^9/L$ . This is often practically unachievable and there are a number of additional factors causing bleeding or thrombocytopenia in these patients such as sepsis, DIC or HLA immunisation due to frequent transfusion. Tranexamic acid can be an additional therapeutic option in addition to correction of obvious coagulopathy with plasma products. Reduction or stopping of heparin therapy is an option in specific cases, however this is potentially hazardous and should only be considered in discussion with the lead clinician looking after that patient.

Currently the NHS specialist commissioning team has increased ECMO capacity across the country to make this treatment available for 100-160 patients a year.

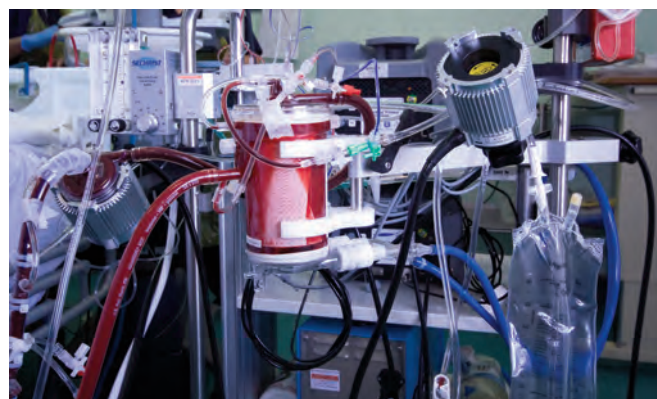
Nationally, platelet demand has increased by 10% over the last three years with the key drivers appearing to be the changes in population demographics (and in particular an aging population) and trends in rates of diagnoses, treatment and procedures that require blood component support.

Anticipating any expected rise in platelet use and applying the necessary marketing and processing activities to meet demand remains a challenge for NHSBT and advance notice of changes in service provision that are likely to impact on blood component demand will greatly help ensuring sufficient supply in the future.

### ECMO Consoles on an ECMO Trolley



### ECMO Pump and Oxygenator and Associated Tubing



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## 2010 Re-Audit of the Use of Group O RhD Negative Red Cells

### Background

Balance between supply and demand of O RhD negative red cells remains a challenge for almost every blood service. In 2008 the Chief Medical Officer's National Blood Transfusion Committee (NBTC) commissioned an audit for the use of O RhD negative red cells in order to understand patterns of its usage. The findings from this audit were widely circulated and discussed at National, Regional and Trust levels. One of the key recommendations of this audit was to aim to reduce O RhD negative stockholding to at least 12% in every hospital by December 2009.

The NBTC issued reviewed guidance in January 2009 and advised hospitals to develop policies allowing the transfusion of group O RhD positive blood to O RhD negative male patients and females without childbearing potential, particularly in the event of massive blood loss. In addition, local stock management policies should be worded so as to minimise the elective transfusion of O RhD negative red cells to prevent time expiry.

The Blood Stocks Management Scheme completed a survey for the prevalence of different blood groups in the hospital population during 2009, and more recently NHS Blood and Transplant (NHSBT) asked hospitals not to hold more than 10.5% of their stocks as O RhD negative in order to be able to respond to escalating demands. Usage of O RhD negative blood for 2011-12 is so far

(November 2011) 11.1% of the total red cells issued. This figure up to 2010 was 10.7%.

### Findings of the Audit

In June 2010 the National Comparative Audit in Blood Transfusion re-audited usage of O RhD negative red cells. The 2008 and 2010 audits are not directly comparable due to the differences in participation and also to the modification of some questions in order to address certain issues more clearly. However some analysis has been undertaken to compare hospitals that participated in both audits and stock holding levels appeared to be reduced in the current audit (although it was not statistically significant).

Only 16% of participating sites keep less than 10.5% of their red cell stocks as O RhD negative. 38% of sites keep stock levels of less than 12% and 15% of sites keep more than 20% of their stocks as O RhD negative. 10% of blood audited in June 2010 was transfused to non O RhD negative patients in order to prevent time expiry. Transfusions to prevent time expiry clearly correlated with stock levels.

Stock levels correlated with the size of hospitals (very low and very high users tend to keep a higher proportion of their red cell stock as O RhD negative red cells). Hospitals keeping more than 20 units in different satellite fridges tend to keep a higher proportion of their red cell stock as O RhD negative. In addition, as was found in the

previous audit, hospitals located closer to blood centres (emergency delivery time of less than 15 minutes) tend to stock much higher levels of O RhD negative red cells.

Emergency units were used in 5.5% of transfusion episodes averaging 2.2 units per episode. In almost 2% of transfusion episodes patients received more than three units of O RhD negative red cells as emergency units. For a third of those episodes, transfusion beyond two units could have been avoided. Following the analysis of patients with alloantibodies and taking into consideration the prevalence of different blood group antigens in the general population, it is possible to identify group specific, phenotypically matched blood fairly easily, particularly for patients of O RhD positive blood group. Provision of group specific phenotyped blood by NHSBT will reduce further unnecessary usage of O RhD negative red cells.

#### **Examples of good clinical practice**

- Hospitals with policies or guidance in place to provide O RhD positive red cells to O RhD negative patients (males and females with no childbearing potential and without anti-D detectable where they were undergoing massive blood transfusion) stock less O RhD negative blood.
- Hospitals able to provide group specific blood in less than 15 min use up to 50% less emergency O RhD negative red cells.

#### **Recommendations**

1. Hospitals must regularly review use of O RhD negative red cells for emergencies and investigate incidents where its use is considered inappropriate.
2. Hospitals must provide group specific red cells rapidly to avoid unnecessary use of emergency group O RhD negative red cells.

3. In some cases in an emergency non RhD negative patients have been transfused with three or more units of O RhD negative red cells. Hospitals should regularly review this practice and keep it to a minimum.
4. For Group O RhD positive recipients with alloantibodies all efforts must be made to identify phenotypically matched group specific blood.
5. NHSBT/Blood services must provide a sufficient number of extensively phenotyped O RhD positive red cells in order to enable appropriate selection of group specific blood for patients with alloantibodies.
6. Hospitals must reduce their stock levels of O RhD negative red cells to the recommended level of 10.5% in order to avoid transfusions of O RhD negative blood to non-O RhD negative patients and thus avoid wastage due to time expiry.
7. Appropriate policies which guide use of O RhD negative red cells should be introduced in order to reduce unnecessarily high stockholding levels.

To see the report of the audit please follow the link:

[http://hospital.blood.co.uk/library/pdf/Re-audit\\_of\\_the\\_use\\_of\\_Group\\_O\\_RhD\\_negative\\_red\\_cells\\_doc\\_2010.pdf](http://hospital.blood.co.uk/library/pdf/Re-audit_of_the_use_of_Group_O_RhD_negative_red_cells_doc_2010.pdf)

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## **Cold Auto Antibodies – What are they, Where do they come from and Why are they Important?**

The term cold auto antibodies or cold agglutinin is somewhat misleading because it implies that the production of these antibodies and the underlying disease has a clear relationship with cold exposure. This terminology is derived from the immunology of cold agglutinin disease which is a form of autoimmune haemolytic anaemia due to cold-reacting auto antibodies. Auto antibodies that bind to the erythrocyte membrane leading to premature erythrocyte destruction (haemolysis) characterise autoimmune haemolytic anaemia. Autoimmune haemolytic anaemia is classified as primary

or secondary; it is sub-classified according to the type of autoantibody.

#### **Causes**

Cold agglutinin disease may be primary (idiopathic) or secondary, caused by infection, systemic autoimmunity, or neoplasm.

Primary (idiopathic) cold agglutinin disease is usually chronic, occurring in adults and no underlying systemic disease explains the presence of auto antibodies.

The auto antibody may be immunoglobulin G (IgG), immunoglobulin M (IgM), or, rarely, immunoglobulin A (IgA); it may be warm reacting or cold reacting. Autoimmune haemolytic anaemia syndromes associated with cold-reacting auto antibodies include cold agglutinin disease (CHAD) and occasionally paroxysmal cold haemoglobinuria. Primary cold agglutinin disease is usually associated with monoclonal cold-reacting auto antibodies.

Secondary cold agglutinin disease, is again usually chronic, occurring in adults, however cases of cold agglutinin disease are also seen in children with B-cell lymphoproliferative diseases, for example, acute lymphoblastic leukemia and may be induced by an associated infection.

- B-cell neoplasms – Waldenström macroglobulinemia, lymphoma, chronic lymphocytic leukaemia, myeloma
- Nonhematologic neoplasms.

Secondary cold agglutinin disease may be acute, transient, and post-infection, occurring in children and young adults.

- Mycoplasma infections
- Infectious mononucleosis due to Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
- Viral infections, including mumps, varicella, rubella, adenovirus, human immunodeficiency virus (HIV), influenza, hepatitis C
- Bacterial infections – Legionnaire disease, syphilis, listeriosis, Escherichia coli
- Parasitic infections – Malaria, trypanosomiasis.

### Frequency

Autoimmune haemolytic anaemia has an annual incidence of one case per 80,000 persons. Cold agglutinin disease may occur in the paediatric population but is more frequent in the elderly population. Secondary cold agglutinin disease associated with infections is the type most commonly observed in children and young adults. Primary cold agglutinin disease is observed in older patients, usually in patients older than 50 years, with a peak incidence of 70 years of age.

Cold agglutinins or cold auto antibodies occur naturally in nearly all individuals. These natural cold auto antibodies occur at low titers, less than 1:64 measured at 4°C, and have no activity at higher temperatures. Pathologic cold agglutinins occur at titers over 1:1000 and react at 28-31°C and sometimes at 37°C.

Cold agglutinin disease is caused by pathologic cold-reacting auto antibodies – usually IgM, occasionally IgG, and rarely IgA. The auto antibodies may be polyclonal,

with the presence of  $\kappa$  and  $\lambda$  light chains, or monoclonal, with a single type of light chain, most commonly  $\kappa$ . Whereas primary cold agglutinin disease is usually associated with monoclonal cold-reacting auto antibodies, secondary cold agglutinin disease may be associated with either monoclonal or polyclonal cold-reacting auto antibodies.

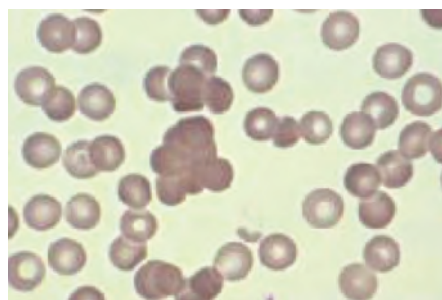
The haemolytic ability of an auto antibody depends on its thermal maximum, the highest temperature at which it binds the antigen on the red blood cells (RBCs). Usually, no agglutination occurs at 37°C. For all cold-reacting antibodies, the antigen with which they react is polysaccharide or the polysaccharide parts of glycoproteins.

### Laboratory Aspects

For cold agglutinins, the antigens are the i antigen, the I antigen, Pr antigens, and rare sialylated polysaccharides. The cold agglutinins of anti-I and anti-i specificity are strikingly similar to one another in the structure of the antigen-binding site. Because the I antigen is not developed until after birth, anti-i auto antibodies predominantly agglutinate neonatal RBCs, and anti-I auto antibodies predominantly agglutinate adult RBCs.

In primary cold agglutinin disease, the RBC antigen target is I. In secondary cold agglutinin disease, the RBC antigen target may be I or i. Less common RBC target antigens include Pr, Gd, M, N, Sdx, and P. Cold agglutinins attach to the RBCs in the peripheral cooler circulation and dissociate from the RBCs as the blood returns to the warmer central circulation. See the image below.

### Blood Film Showing Spherocytic and Agglutinated RBCs



Autoimmune haemolysis is due to complement fixation. Fixation of auto antibody and complement occurs intravascularly when the blood temperature drops below the thermal maximum of the antibody. This can occur if the antibody has a high thermal maximum or if the patient is exposed to a colder environment.

Extravascular haemolysis occurs when activation and fixation of complement to the RBC membrane is

insufficient to trigger activation of the membrane attack complex of complement. C3b and C4b present in the RBC surface interact with receptors in the phagocytes of the lungs, liver, and spleen, and the RBC is phagocytised. The liver is the predominant site of haemolysis.

### **Problems**

Blood grouping and compatibility testing is performed in the event that a transfusion is needed and auto antibodies may interfere with compatibility tests. The auto antibody may react with the RBCs of all potential donors, making it difficult to detect underlying alloantibodies, which is the priority for providing blood for patients. Several techniques are available to improve compatibility testing. These techniques include testing the patient's plasma for anti-A and anti-B hemagglutinins and performing the compatibility testing (ie antibody identification and cross-matching) at 37°C, so that the cold antibody disappears and underlying alloantibodies can be identified. Other strategies include the use of Rabbit Erythrocyte Stroma (RES) to remove the auto antibody rendering the plasma suitable for testing to identify underlying alloantibodies to RBCs. Other approaches include the use of Dithiothreitol which can be used to denature the IgM autoantibody, again to render the plasma suitable for conventional compatibility testing.

The Direct Antiglobulin Test (DAT) is usually positive with anti-C3 and negative with anti-IgG. The DAT may be positive for immunoglobulin M (IgM), but mixed immunoglobulin G (IgG)/IgM and occasionally immunoglobulin A (IgA) is seen.

Transient cold agglutinin disease is characterised by a moderately elevated cold agglutinin titer (1:1,000-20,000) and polyclonal cold agglutinins.

In chronic cold agglutinin disease, the cold agglutinin titer is very high (>1:100,000-1,000,000), and the cold

agglutinins are monoclonal. In chronic cold agglutinin disease associated with monoclonal gammopathy and with chronic lymphocytic leukaemia, the auto antibodies are monoclonal anti-I. In chronic cold agglutinin disease associated with malignant lymphomas, the auto antibodies are monoclonal anti-i.

The auto antibodies are more reactive in the cold with diminishing reactivity as the temperature approaches 37°C. Indirect antiglobulin test results at 37°C are negative.

For the purposes of providing safe blood, provided the cold antibody is not reactive at 37°C, corresponding antigen negative blood is not required: ABO, Rh and K compatible units are provided. Rarely, in a case where transfusion has given no response with P+ blood in a patient with anti-P, P-blood from the National Frozen Blood Bank in Liverpool may be indicated. In practical terms, for hospitals unable to perform testing at 37°C (eg using gel cards, where some are unable to warm everything adequately to 37°C), additional time for referral would be required before blood can be provided. The need for the use of blood warmers in cold agglutinin disease is open to debate but may be of some benefit.

In summary, cold agglutinin disease and the cold antibodies characteristic of the disease present particular challenges for the Hospital Transfusion laboratory and the National Transfusion services in terms of laboratory testing and provision of suitable blood for transfusion.

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## **Platelets Across the Border – A Multiple Disciplinary Collaboration Between Transfusion Services to Supply HPA Selected Platelets**

Many staff will be familiar with the provision of HLA selected platelets which are frequently provided for patients recovering from intensive chemotherapy and bone marrow transplantation. There are also circumstances when it is necessary to provide platelets that are compatible with antibodies against human platelet antigens (HPA). Typically, these platelets are required for babies or fetuses where the mother has become immunised against HPA during pregnancy. This is

the platelet equivalent of haemolytic disease of the newborn and is known as neonatal alloimmune thrombocytopenia (NAIT). These babies often have a low platelet count and the associated risks of life threatening bleeding and permanent disability.

In order to manage cases of NAIT, NHSBT has identified a small cohort of about 120 'accredited donors' that have a HPA type that are compatible with the HPA-1a and 5b antibodies that together account for 95% of

NAIT cases in the UK. However, there are rare cases of NAIT due to other antibodies and if the HPA involved has a high frequency, it can be particularly difficult to find suitable donors.

In November 2010, the Histocompatibility and Immunogenetics (H&I) Department in Filton was contacted by the Scottish National Blood Transfusion Service (SNBTS) in Dundee to provide platelets for the baby of a pregnant woman that was due in mid-January 2011. This woman had a history of NAIT due to both HPA-1a and HPA-5a antibodies and her first baby had a delivery platelet count of  $3 \times 10^9/L$ , an intracranial haemorrhage and subsequently died. There were no HPA compatible platelet donors in Scotland. H&I searched the database for HPA typed platelet apheresis donors in England and found only a *single* donor that had the correct HPA type (i.e. HPA-1b1b, 5b5b) that was also CMV negative (another requirement for transfusions to newborn babies).

The race was then on to arrange additional testing to ensure suitability for the baby and schedule a donation from this unique donor in case the platelet count of the baby was low at delivery. H&I in Filton contacted the component donation unit in Sheffield where the donor attended and they contacted him to determine his availability to donate a few days in advance of baby's scheduled arrival. The donor also provided samples for additional testing to ensure that there were no antibodies in his blood that might adversely affect the baby. H&I in Sheffield were also informed to ensure that this donor's platelets would not be used to support another patient.

With all additional tests on the donor completed satisfactorily, the platelet donation was collected on the appointed day and moved from Sheffield to Newcastle, while Hospital Services in Sheffield completed the mandatory tests. The units were split and irradiated into neonatal packs in Newcastle, transferred to Edinburgh, logged into the SNBTS computer system and transferred to Dundee in time for baby's arrival.

The baby was delivered on schedule on the 14th January. The baby's platelet count was low ( $62 \times 10^9/L$ ) on delivery but not dangerously so – the mother had received IVIgG treatment during pregnancy which seemed to have been effective. The baby's platelet count spontaneously increased to  $171 \times 10^9/L$  (17th January) and then to  $238 \times 10^9/L$  (19th January). Ultimately, the infant did not require a platelet transfusion. However, the previous eight weeks of planning illustrate the excellent cooperation between a multidisciplinary team consisting of Histocompatibility and Immunogenetics, Component Collection, Hospital Services and Transport collaborating across two Transfusion Services in making a unique product available to ensure a favourable outcome for the patient. Of course, the most important element of all was the motivated donor, who declared that he was *"...proud and happy that he could help."*

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## HIV Lookback Audit in England and Wales: 1995-2009

### **Background**

Lookback is the term used for the investigation of previous donations from a donor who is newly found to be infected with a transfusion-transmissible infection. The term first came into use when HIV screening of blood donations started in 1985, with the recognition that previous untested donations from HIV infected donors could have been capable of transmitting HIV infection, since the donor may have been infected for some time.

It has now been over twenty-five years since routine screening of blood donations for HIV began and during this time testing methodologies have progressively improved. The introduction of combined antigen/antibody (Ag/Ab) assays and mini-pool NAT testing has provided enhanced testing performance, increasing sensitivity and shortening the infectious window period (IWP) where

donations are infectious but have negative test results from 15 days to 9. There has been a resultant decline over time in the probability of an HIV infectious donation entering the blood supply.

When HIV infection is newly detected in a blood donor who has made previous donations (a seroconverter), lookback to the donor's most recent previous negative donation (MRPND) by NHS Blood and Transplant and Welsh Blood Service clinical departments is considered. Lookback can include all or any elements of the following: retrieval and re-testing of an archive specimen from the previous negative donation(s) using the most sensitive tests available, investigation of the fate of any components from previous donations and, through liaison with transfusion practitioners at hospitals, the identification of recipients of those components, notification and the offer of testing of living recipients.

The rationale for lookback is that, although rare, it is possible that the previous donation was infectious but not detected through testing because the donor donated in the IWP or the assay produced a false negative result; re-testing of the archive specimen using genomic testing eliminates a false negative result while follow-up of components and recipients allows for tracing should a donation have been made in the IWP. Lookback can lead to the identification of HIV infected recipients earlier than would otherwise happen, enabling referral for specialist care, and advice to prevent onward HIV transmission.

### **Data Collection**

In August 2002, a surveillance programme to collate information on lookback for previous donations from HIV seroconverters was set up within the joint NHSBT/Health Protection Agency Epidemiology Unit in collaboration with NHSBT Transfusion Microbiology clinical staff. Data was collected retrospectively for HIV positive donors identified from October 1995 and prospectively from 2002 onwards. Information was collected on the testing of archive specimens, including the assays used and the results, the fate of any previous donations and follow-up of recipients. If no lookback was undertaken, information on the rationale for this decision was provided.

### **Results**

Between 1st October 1995 and 31st December 2009, 140 HIV infected donors with previous negative donations were identified and were eligible for inclusion in the lookback study; investigations were undertaken in 122 cases. Full details of these investigations (to December 2008) have recently been published and are summarised in Figure 1 (on page 15). In 114 cases where an archive specimen was available and re-tested negative, no evidence of transfusion transmitted (TT)-HIV was established among the 55 recipients who were alive and tested. Two previous screen negative donations, given prior to the introduction of mini-pool NAT (MP-NAT) screening, were confirmed positive by individual retrospective PCR testing of the archive specimen. Red cell components had been transfused from both donations. One recipient had died post transfusion; the other was alive and tested HIV positive.

### **Conclusions**

During fourteen years of surveillance, lookback identified one confirmed HIV transmission and one presumed HIV transmission through blood transfusion in England and Wales, in one living and one deceased recipient respectively. In both instances, the donor's MRPND donation had been given during the infectious window-period prior to production of detectable antibodies. Both donations pre-dated the introduction of MP-NAT for routine blood donation screening. Both archive specimens, when tested retrospectively using PCR, were confirmed HIV RNA positive and would have been detected if NAT screening had been in place at that time; under current testing protocols these donations would have been detected by HIV-NAT testing and would not have been issued for use.

There has been one other documented case of TT-HIV reported to the UK's haemovigilance scheme, Serious Hazards of Transfusion (SHOT) since its establishment in 1996. This case was identified through investigation of a recipient, transfused in 1996, who developed signs of HIV infection some months after transfusion. The donation was made by a repeat donor, who had not donated subsequently so had not been identified through donation testing. Lookback does not identify donors who seroconvert after donation if they do not return to donate and it is important to maintain the investigation of post-transfusion infections and trace-back to maximise identification of TT-HIV cases. There have been no other TT-HIV cases confirmed through trace-back or linkage with GUM services since 1995, and only one other documented case of transfusion-transmission of HIV in the UK prior to the establishment of SHOT, also detected by lookback.

The overall yield of lookback in England and Wales was low, with just one HIV positive recipient identified from 122 lookback investigations over a fourteen year study period and reflects the low TT-HIV risk in the English and Welsh blood supply. The introduction of combined antibody-antigen tests followed by MP-NAT screening, has improved the safety of the blood supply and reduced the already low risk of HIV transmission through blood transfusion in the UK, demonstrated by the lookback study and haemovigilance reports. HIV lookback and its surveillance continues.

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### **Acknowledgements:**

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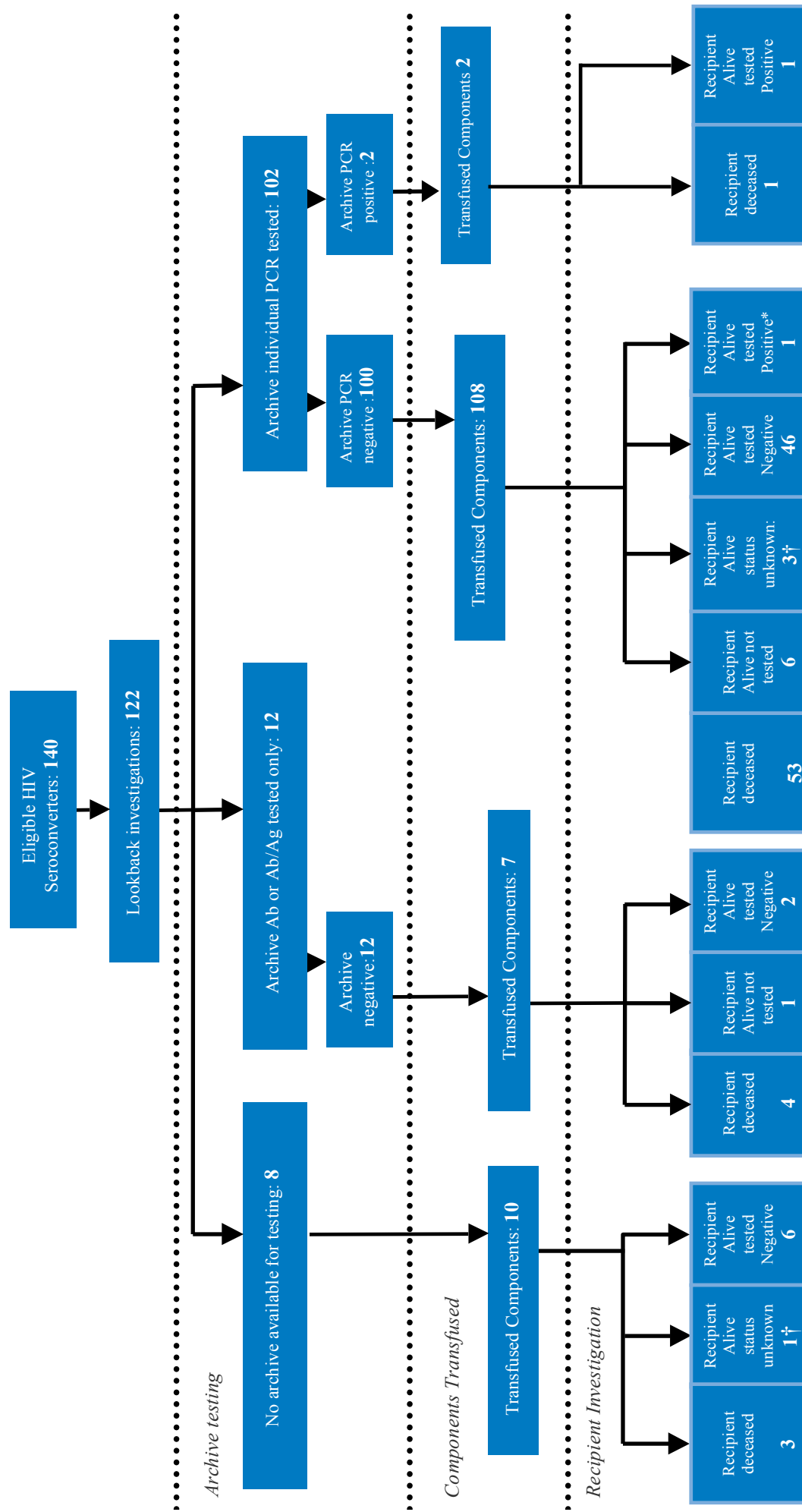
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**Figure 1. Summary of HIV Lookback Investigations, England and Wales, October 1995 through to December 2009**



\* This figure includes one recipient who was known to be positive pre-transfusion. Recipient testing pre and post transfusion confirmed no transmission from the blood donation. The recipient was antibody positive only.  
 † Status unknown as it was not reported back to the blood services despite repeated requests.  
 ‡ Confirmation on any Look-back is awaited for two eligible cases which are not included here.

# Significance and Measurement of Human Leukocyte Antigens and their Antibodies

## Part I: Clinical Importance of HLA and their Antibodies

### Introduction

Human Leukocyte Antigen (HLA) is the collective name for a large group of related proteins found on the surface of nearly all nucleated cell types in the body (ie not just blood leukocytes – an historical misnomer). These also go under the name *Transplantation Antigens* which, although not completely inaccurate in terms of their clinical significance, rather underestimates their biological role as molecules central to the presentation of foreign antigens to our immune system and its regulation. Most cell types involved in immunity (such as T cells, natural killer cells and macrophages) carry receptors that bind HLA. This is one of the two principle reasons behind HLA being the major transplant antigen – they are directly targeted by the immune system and rejection is an immunological process. The second reason is the genetic diversity of HLA; many immune system proteins are genetically variable, most likely due to an evolutionary arms race with viruses and bacteria, but HLA has done this to an extreme degree.

### Genetic Complexity of HLA

There are two broad groups of HLA; class I and class II. There are three members of the class I group; HLA-A, B and C, and there are three members of the class II group; HLA-DR, DQ and DP. For each of these six distinct proteins (there are in fact more than six but the others may have slightly less clinical significance in transplantation and transfusion) there are multiple genetic forms. For example, for HLA-A alone there are over 1,000 genetic forms. Table 1 demonstrates the degree of genetic variability in the HLA system (Class I HLA have a single polymorphic chain whereas Class II molecules are  $\alpha\beta$  heterodimers determined by A and B genes, respectively; for DQ and DP both genes are polymorphic). An allele is defined as an alternative version of a gene with a unique DNA sequence. The numbers of different proteins determined by each locus are given; these are lower than the number of alleles, the difference being due to silent DNA substitutions and null (non-expressed) alleles. Together there are over 5,000 different genetic forms amongst the six groups. We usually inherit a set of HLA from each parent (ie twelve genes producing twelve proteins), and collectively this forms a *tissue type*. Given the variation amongst HLA genes and the number each of us carries, the number of different combinations reaches many millions. This means

that two randomly selected individuals will almost certainly have different HLA types, but within families there is obviously a much greater chance of finding HLA matched individuals.

**Table 1. Current numbers of recognised HLA alleles**

(Source: IMGT/HLA database at <http://www.ebi.ac.uk/imgt/hla/stats.html>).

HLA Locus	Alleles	Proteins
A	1,698	1,243
B	2,271	1,737
C	1,213	884
DRB1	975	736
DQA1	44	27
DQB1	158	109
DPA1	32	16
DPB1	149	129

### Stimulation of HLA-Specific Antibodies

When tissues are transplanted or transfused from one individual to another and if there are HLA mismatches between the two, which is more than likely, then the recipient can mount an immune response against the donor's different HLA. The response usually includes the development of antibodies which can be detected in serum or plasma. Such a response does not always occur, but when it does a further transfusion or transplant could result in immediate rejection of the tissue. The normal, physiological cause of HLA sensitisation occurs during pregnancy because the paternal HLA is bound to differ from the mother's. With successive pregnancies (with the same father) the chance of the mother producing HLA specific antibodies increases. There is very little evidence that these maternal antibodies ever damage the foetus in the way, for example, that antibodies against paternal Rh or platelet-specific antigens (HPA) can cause life-threatening disease, even though HLA is expressed on foetal tissue, including platelets. It is possible that widespread HLA expression by placental cells absorbs HLA specific antibodies thus protecting other foetal tissues.

Blood transfusion is also capable of stimulating HLA antibodies. Even with universal leucodepletion there are still enough residual cells for the transfusion to be

immunogenic and there will also be some soluble HLA in the plasma and certain HLA forms can be adsorbed onto red cells (and there constitute the Bg blood group system). The more transfusions a patient receives, the greater the chance of sensitisation causing HLA specific antibodies.

### **Significance of HLA-Specific Antibodies in Transplantation and Transfusion**

Previously stimulated HLA antibodies can be very harmful to subsequent transplantation or transfusion of certain blood products. Immunosuppression is used in transplantation to prevent rejection mediated by the cellular immune system but is generally ineffective at preventing rejection caused by pre-existing donor HLA-specific antibodies. A kidney transplanted against donor specific antibodies is likely to suffer early rejection; if the levels are high then the rejection will be immediate (hyperacute rejection) and the patient will have to return to dialysis. Hyperacute rejection of a heart transplant invariably means death of the recipient. In the transfusion of HLA sensitised patients the most significant problem occurs with those requiring platelets. Even though red cells can carry adsorbed HLA, transfusion reactions mediated by HLA specific antibodies are of no concern, although these antibodies can agglutinate red cells in vitro and are more of a nuisance to interpretation of the reactions of samples with complex mixtures of red cell antibodies than anything else. Platelets, however, are rich in HLA class I expression, but not class II. Patients with low platelet counts are prone to internal bleeding, which can be fatal, and this can be treated with platelet transfusions. Antibodies against the platelets will cause immediate removal of the transfused platelets from the circulation and their destruction. This is termed immune platelet refractoriness, the platelet count remains low and any bleeding will continue. HLA specific antibodies have recently become a problem in haematopoietic stem cell transplantation (HSCT) because of the increasing use of HLA mismatched donors. Previously full HLA matching of donors and recipients had always been advised because of the high risk graft rejection and fatal graft vs host disease. HSCT using cord blood has now become widespread because of the rapid access to stored donations and the development of protocols that allow good outcomes with even poorly matched donors. There is some evidence that donor HLA directed antibodies in the recipient can reject these transplants, presumably much in the same way as platelets can be rejected, or perhaps inhibit engraftment.

HLA specific antibodies are therefore of clinical significance in a variety of settings: their detection and characterisation is an important laboratory activity in support of transplantation and transfusion. As we have learnt of the complexity of the HLA system it has become clear that this is matched by the complexity of their antibodies. This increasing clarity has been made possible by recent technological developments in the field of antibody testing which not only give better and quicker results than before, but also improve our understanding of how to use this information in the treatment and monitoring of patients. Part II of this article will describe methodologies and how the information available from contemporary techniques can improve access to treatment as well as provide insights into the immune system.

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## Selection and Allocation of Solid Organs for Transplantation

One of the statutory roles of NHSBT is the selection and allocation policies for organs donated by deceased donors. Selection relates to who gets on to the national transplant list and allocation relates to who gets the donated organ. In contrast to organs donated by living individuals, which are controlled by the Human Tissue Authority, organs donated by deceased donors must be donated without pre-conditions and we cannot accept organs donated with any restriction on their use. Thanks to a recent change in the regulations, families can ask for directed allocation, where organs from a deceased donor can be allocated to a named individual such as a member of the family, who is on the national transplant list. In this brief review, some of the issues affecting the development of these policies are mentioned.

Because of the shortage of organs, not all those who could benefit from a transplant can receive one so there has to be rationing of this life-saving resource. Developing policies that are acceptable has been and remains, a challenge. Although the development and implementation of these policies is the responsibility of NHSBT, we work very closely with the solid organ Advisory Groups to agree the principles of selection and allocation and I would like to take this opportunity of thanking all those who, over the years, have contributed so much of their time to the development, review and revision of these policies. The policies are developed after discussion with patients and patient groups and, when agreed by the Advisory Group, are reviewed and approved by a sub-group of the NHSBT Board, the Transplant Policy Review Group, chaired by a non-executive director.

Policies have to be transparent so they are understood and supported not only by those health care professionals who follow them but also the public, including the potential donors, their families, patients and other interested parties. While the clinician will do their best for their patient, the shortage of donated organs means that allocation of a donated organ to one, will deny another of life-saving surgery. Policies should be evidence-based, where possible, and consistent with legislation. This has generated challenges: for example, studies have shown that both the public and the professionals would give priority to children, although this may fall foul of legislation on age discrimination.

**Selection:** selection can be based on listing all those who might benefit from transplantation, with respect to improving either quality or quantity of life (or both). This approach will result in a long list and many people will have no realistic expectation of getting a graft; a large list

is also difficult to manage. An alternative approach is to restrict access to the list to those who are likely to get a graft: this approach not only gives a severe underestimate of the need for transplantation but also generates a challenge as to the criteria for selection.

**Allocation:** there are several principles on which allocation policies can be based:

- Utility: where the aim is to allocate the graft to the individual with the greatest survival.
- Benefit: where the organ is allocated to the individual with the greatest benefit, so taking into account the survival with and without transplant.
- Equity: this concept is less easy to define and often means different things to different people: for example, does equity mean that all potential candidates will have the same chance of getting a graft irrespective of age, outcome or indication or does it just mean that all patients with a given demographic will have the same chance of being offered a graft?
- Minimum benefit: should there be a minimum benefit? Many administrations have accepted a concept of minimum benefit to avoid futile transplants. Although the most commonly accepted minimum benefit is an expected survival probability of at least 50% at five years, with a quality of life acceptable to the patient, this is not based on any data but seems clinically sensible.

Of course, there are other issues: should waiting time be considered in the allocation process? How do you decide whether to allocate a graft to someone who is dying from end-stage organ failure with another candidate whose life is intolerable because of consequences of organ failure? How do you decide whether to allocate a graft to someone who has lost their first graft because of non-compliance or to another who requires a graft because of behavioural pattern (such as previous intravenous drug use) or to another who has never had a graft? Should organs be allocated to a centre or an individual? Advantages of a national allocation system is that it is transparent, objective and accepts that donated organs are a national resource; on the other hand, allocation to a centre allows the clinicians to use their knowledge of the individual patients and clinical judgement as to the most appropriate candidate for that particular organ.

All these policies are dependent on the knowledge of those factors that are associated with survival with and without a transplant and the establishment of robust, validated prognostic models. While the Directorate of

Statistics and Clinical Audit has a well-deserved international reputation in this area, models are still relatively broad; we still do not understand sufficiently those donor and recipient factors, or their interaction, which determine outcome, in the short or long term.

There are no simple answers to the best solution: all allocation policies are a compromise. Because different factors affect different systems (for example, there is no equivalent to dialysis for those in liver or heart failure), there are different principles adopted for different organs. It must also be recognised that while implementation of robust selection and allocation policies will ensure, as far as possible, transparency and equity (however it is defined!) the policies must be audited to

ensure the aims are met, as well as being sufficiently flexible to allow innovation and development.

Thus although we do have robust systems for developing and implementing selection and allocation policies, it remains a fascinating challenge to ensure that these remain appropriate and relevant and supported by all involved in the transplantation process.

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## Transplantation for Diabetes – The Place of Islet Transplants

Effective treatment of Type 1 diabetes has been available for almost 90 years, but the life-long treatment needed is associated with a spectrum of complications that is now very familiar – retinopathy, nephropathy, neuropathy and a very high incidence of cardiovascular disease. In addition, some patients are remarkably difficult to manage with insulin – swinging between hypoglycaemia and hyperglycaemia – and others suffer from life-threatening ‘hypoglycaemic unawareness’ (lack of warning of an impending hypoglycaemic event).

Pancreas transplantation was first attempted in 1967 but the early results were poor, for many reasons including technical complications (venous thrombosis was common), rejection, sepsis and pancreatitis. A number of transplant units around the world persevered during the 1970s and 1980s, testing different immunosuppressive regimes, preservation methods and surgical techniques. By 1990 the results were improving and it became clear that there was a place for transplantation of the pancreas in selected patients in whom the benefits were greater than the risks.

The diabetic patients to whom this applied were, and predominantly remain, those with chronic renal failure secondary to diabetes. Diabetes is one of the commonest causes of chronic renal failure and such patients have long been regarded as suitable candidates for kidney transplantation. Although the outcome of transplantation is poorer in diabetics than that in patients with other aetiologies of chronic renal failure, the quality of life and life expectancy are nonetheless significantly superior to those of patients remaining on dialysis. Many patients with diabetic renal failure are, thereby, already committed to the long-term risks of immunosuppression and the risk of pancreas transplantation is therefore an incremental

increase, based on the complications specific to the pancreas. Over the last 20 years, pancreas combined with kidney transplantation has become the treatment of choice for many patients with diabetic renal failure. Evidence from large registries and unrandomised clinical trials shows that successful pancreas transplantation not only increases life expectancy, but also stabilises or improves secondary complications in many patients. The morbidity remains significant, however, and a risk-benefit analysis for each patient is still an essential part of assessment.

The situation is less clear for patients without renal failure. In patients selected for pancreas-only transplantation because of severe non-renal diabetic complications, long-term graft survival is lower and there is less evidence of benefit. Essentially, the risk of postoperative complications is similar to the combined (pancreas and kidney) operation but the benefit is less.

Much of the early morbidity of whole organ pancreas transplantation is associated with the exocrine function of the gland. The endocrine component, situated in the Islets of Langerhans, constitutes only 2% of the pancreas by volume and it has long been argued that it is logical to extract and transplant just the islets from a donor pancreas. This strategy, very simple in concept, has proved remarkably difficult to achieve in practice. Many difficulties have been faced since the first attempted clinical transplants in the 1980s. These include: the technical challenge of isolating undamaged islets from the donor pancreas; the optimum means of preservation; the best site for implantation; the most effective immunosuppressive regime.

Although good experimental results caused optimism, clinical results were poor in the 1990s with only a minority of patients showing evidence of medium-term insulin production and very few patients remaining insulin-independent for any useful period. A step-change occurred in 2000 with the publication of a series of seven patients in Edmonton, Canada, who were rendered insulin-independent by islet transplantation. This was achieved by a number of innovative steps, including the use of sequential transplants (multiple donors) and the use of a novel immunosuppressive regime. These results were soon replicated in leading centres in several countries, but longer-term results remained disappointing with published five-year insulin dependence rates of 25% or less. However, the most recent results suggest that with further innovation in immunosuppression, five-year insulin independence can be achieved in 50% of patients – this is moving close to the outcome of solid organ transplantation.

Despite concerns that long-term insulin-independence rates have not compared favourably with isolated solid organ transplantation, for a number of reasons there is growing interest in the application of islet transplantation: First, the morbidity of islet transplantation is very much less than that of whole organ transplantation – without most of the major problems associated with graft thrombosis, reperfusion pancreatitis, exocrine leakage etc. Failure of an islet transplant is signalled by lack of function rather than any life-threatening complication. Islets are transplanted by infusion into the portal vein, accessed by a radiological

trans-hepatic approach; this has a low complication rate (although bleeding from the liver and portal vein thrombosis are recognised hazards).

Second, although many patients never achieve insulin-independence, or achieve this only temporarily, many more maintain a functionally-useful level of insulin production (assessed by C-peptide levels). This is often adequate to transform the diabetic management of a patient with hypoglycaemic unawareness. It is these patients for whom islet transplantation is most valuable and for which it is specifically indicated.

Islet transplantation is available as an NHS service throughout the UK. Three centres are responsible for islet isolation and a network of seven centres is responsible for providing assessment, transplantation and follow-up. Patients awaiting both islet and solid organ pancreas transplants are placed on a single national waiting list and donor organs are allocated according to a complex algorithm.

Islet transplantation is appropriate to selected patients with hypoglycaemic unawareness who have failed trials of conventional insulin-delivery systems (including insulin pumps). It may also be offered to patients with diabetes with previous and still-functioning kidney transplants.

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## The National Scheme for Paired Living Kidney Donation

### **Background**

Living donor kidney transplantation has increased markedly in the UK in recent years and in 2010/11, 38% of the 2,687 kidney transplants performed were from living donors.

Many candidates for kidney transplant have family members or friends who are willing to donate, but it is estimated that around one third of potential living donor transplants cannot proceed with a straightforward transplant because of ABO blood group incompatibility or human leukocyte antigen (HLA) sensitisation of the recipient. In these circumstances a number of possibilities can be considered. One option is for the patient to wait for a deceased donor transplant, although the median waiting time is three years, with no guarantee of a suitable donor being found at all. Another option is for the patient to proceed with an incompatible transplant

with their donor. This is a complex procedure that is not possible for some donor-patient pairs and has uncertain long-term outcomes. A further option was made possible by the Human Tissue Act 2004 and the Human Tissue (Scotland) Act 2006 which allowed paired donation to commence in the UK. A national scheme enables incompatible donor-recipient pairs to exchange kidneys with others in the same situation, so that recipients can receive alternative, compatible living donor organs.

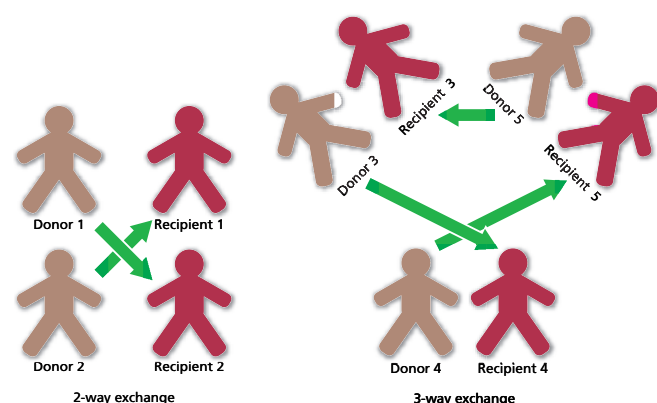
The national scheme is managed by NHS Blood and Transplant. Pairs must be fully worked up and ready to proceed with a transplant before they are registered, and every three months a computerised 'matching run' is carried out to identify and prioritise possible exchanges. Exchanges are identified between two or three incompatible pairs (see Figure 1). Transplant centres are then notified of the results so that tests can be carried

out to confirm compatibility between the matched donors and recipients. Pairs must also be seen by an Independent Assessor, after which approval for the transplant must be gained from the Human Tissue Authority.

### **Growth of the Scheme**

There were eight pairs in the first matching run in April 2007, and two transplants were identified and went ahead in July 2007. Since then the scheme has increased to approximately 200 pairs per matching run and a total of 108 patients had received a paired living kidney donor transplant by the end of July 2011. Such transplants represented 4% of the 955 living kidney donor transplants in the UK in 2010/11.

**Figure 1: Two and three-way exchanges**



Since the scheme started, almost 500 pairs have been registered and over 200 transplants have been identified. Unfortunately, 50% of the identified transplants have not proceeded for reasons that include positive crossmatch tests (demonstrating incompatibility that was not anticipated), donors or patients being found to be unfit for transplant and patients withdrawing due to other transplant options (deceased donor offer, incompatible transplant). These issues impact on other donors and recipients in the exchange group, leading to delayed or missed opportunities for transplant, and thus education has been improved and changes made to the scheme to help improve the transplant rates.

### **Transplant Success**

Of the 108 transplants to the end of July 2011, 60 patients successfully received a transplant through two-way exchanges and 48 through three-way exchanges. Many other registered pairs were transplanted as a result of an offer of a deceased donor kidney (most patients are simultaneously registered for deceased donor transplantation) or due to an incompatible living donor transplant, often planned after no suitable transplant has been identified in a number of successive paired donation matching runs.

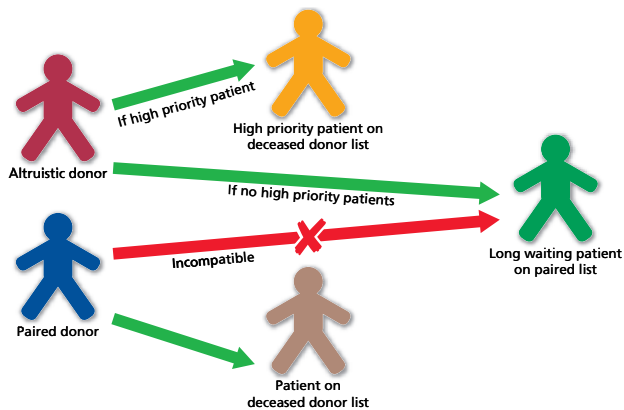
The scheme's success in identifying possible transplants is somewhat limited by the generally high levels of sensitisation in patients registered. Over 50% of the patients registered for each run have a calculated sensitisation level (or HLA antibody reaction frequency) of at least 95%, indicating that at least 95% of blood group identical donors will not provide a match because of the patient's antibodies, produced largely in response to previous transplantation. Nevertheless, 3% of this extremely complex group of patients have successfully been transplanted through the scheme, with much greater levels of success for those with moderate levels of sensitisation (31% of those with 10-84% sensitisation and 21% of those with 85-94% sensitisation). For those pairs with blood group incompatibility, donor A – recipient B and donor B – recipient A are the most successful in finding a match (27% and 29% transplanted, respectively). Very often these pairs are matched together to achieve a simple two-way exchange with no sensitisation to add complications. HLA incompatible pairs where the donor is blood group O and the recipient is A are the most successful blood group combination, with 42% of such pairs achieving a transplant through the scheme.

On the day of transplant, operations are carried out simultaneously in the two or three hospitals involved. The kidneys are removed and transported quickly to the recipient's hospital where they are transplanted, typically within five hours.

### **Future Potential**

In order to increase the potential of paired donation, other countries, such as the US and the Netherlands, have implemented what is known as domino paired donation or altruistic donor chains. This involves an altruistic living donor – someone who wants to donate a kidney anonymously to a stranger. In the UK, kidneys from these donors are currently allocated to the most appropriate recipient on the deceased donor transplant list. However, by donating their kidney into the paired donation pool, one or more paired donations can be triggered, involving a donation back to the deceased donor list. This approach has been agreed in the UK and will be implemented for the first matching run in 2012 (see Figure 2), ensuring that high priority patients on the deceased donor list continue to take precedence (likely for 8% of altruistic donor kidneys). This change will mean a greater chance of transplant for the many very difficult to match patients on the paired donation list, particularly as priority will be given to those having been through the most previous runs.

Figure 2: Altruistic donor chain



## Summary

Kidney paired donation has been successfully introduced in the UK with 22% of registered pairs achieving a paired donor transplant, but it is anticipated that combining the programme with altruistic non-directed living kidney donation, which has seen 80 living donor transplants in the first four years, will increase markedly the efficacy of both programmes and continue to expand living kidney donor transplantation in the UK.

**Rachel Johnson**

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**Statistics and Clinical Audit**

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## Ex-Vivo Lung Perfusion and its Implications for Pulmonary Transplantation

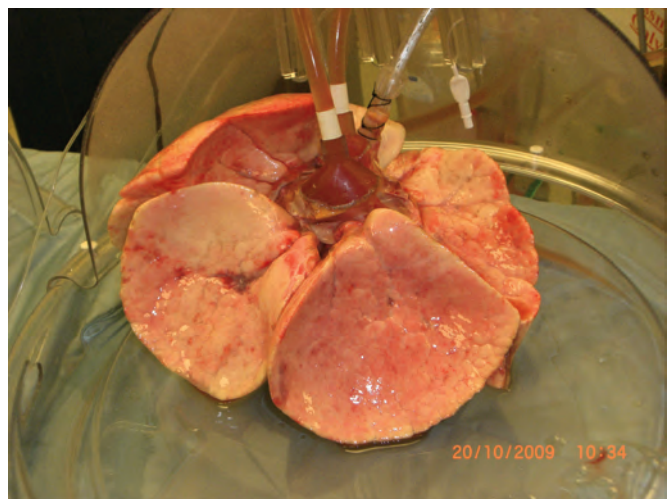
Transplantation of the lung is now a very successful treatment for many patients with end-stage respiratory disease. There have been great advances since the technique was introduced nearly 25 years ago, but activity is still modest. For example, the transplant programme at the Freeman hospital is the most active in the UK, but only performs 40-50 procedures per year. There is a 20% mortality on the waiting list, rising up towards 30% for those with cystic fibrosis. However, after transplant, there is better than an 85% one-year survival, and in the long term, more than 50% of younger recipients are surviving 10-11 years.

The rate limiting step is the availability of donor lungs which can be relied upon to function well after transplant. There are approximately 650 heart-beating organ donors a year in the UK, with, in 2010-11, another 350 non-heart beating, or DCD (Donation after Circulatory Death). But only 15-20% of donors have lungs which *currently* can be used; for non-heart beating donors the figure is less than 10%. The principle reason for this low uptake is that there is frequently a degree of damage and dysfunction in the donor lung. In addition to insults such as trauma, aspiration, multiple blood transfusions and prolonged ventilation, the process of brain death has many additional effects. There is a haemodynamic, stress injury, probably responsible for "neurogenic pulmonary oedema", and a subsequent inflammatory up-regulation. We have shown in humans that there are elevated levels of pro-inflammatory cytokines in donor lungs, and ischaemia/reperfusion amplifies pre-existing damage.

A method of improving the condition of the lung is to take it out of the milieu of the donor, gently ventilate and

perfuse with a hyperosmolar solution free of white cells, platelets and complement. Collapsed areas can be re-inflated and airway secretions thoroughly removed. Very high-dose antibiotics can be given, and we have shown a thousand-fold reduction in microbiological load.

A number of centres around the world are working on this concept, and globally more than 65 patients (including seven in Newcastle and others in Harefield, Papworth and Wythenshawe Hospitals) have had successful transplants using lungs treated with this Ex-Vivo Lung Perfusion (EVLP). The largest published series is from Toronto, with 21 successful transplants out of 23 lungs assessed. None of these lungs could have been used for transplant using conventional criteria.



Two lungs on the circuit are shown in the photo, with cannulae attached to the left atrium and pulmonary artery, and an endotracheal tube in the airway.

This technique also allows for objective assessment of the donor lung, with measurements of gas exchange (by perfusion with de-oxygenated solution), pulmonary artery pressures and flows, static and dynamic compliance and permeability. Indeed, part of the impetus behind this development was to permit safe clinical use of lungs from non-heart beating donors, in whom physiological data, in the absence of a circulation, is difficult to obtain.

Finally, EVLP gives an opportunity to manipulate aspects of lung injury, to improve the condition of the lung before implantation. In the limited clinical experience, only about 50% of human donor lungs perfused improve to the point where they can be used for implantation. There is a huge need for investigation of manoeuvres such as free-radical scavenging, addition of surfactant protein or blocking of pro-inflammatory pathways (for instance, by IL8 antagonists) to improve the yield.

What then, is the likely impact on lung transplantation in the UK? We might double the number of lung transplants from brain-dead donors, by converting the marginal to the readily acceptable. Many more lungs from DCD donors might be transplanted – in the Netherlands they already comprise 30% of all transplants, even before using this technology.

The technique is not without costs – disposables and perfusion fluid amounts to £3-4,000 per case, and there is a burden of staff time supervising the lungs during perfusion. A national UK study including all five transplant centres is planned to evaluate the costs and benefits of the whole approach.

Perhaps the most exciting prospect is the use of lungs from the so-called “uncontrolled” DCD donors. These are patients who suffer sudden death, usually of a cardiac cause, and cannot be resuscitated. In the absence of any brain trauma, the lungs should be almost undamaged, but of course they are a completely unknown quantity, with no previous information. EVLP gives us a unique method to assess these lungs. A pilot study will begin shortly in Newcastle, funded by NHSBT through a competitive bidding process. It is exciting because there are potentially **10** times as many DCD donors of this type as there are conventional brain-dead donors. If this approach works, it will transform clinical lung transplantation.

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## “Do You Know Who I Am?” Patient Awareness Campaign

### **Background**

Serious Hazards of Transfusion (SHOT) was established in 1996 and is the United Kingdom’s professionally led haemovigilance scheme for the reporting of transfusion related adverse incidents and reactions. SHOT collates the data sent to them and provides an annual report with recommendations designed to improve transfusion practice. Patient misidentification errors were found to be the cause in 52 incidents reported to SHOT in 2009. This is despite transfusion training and the NPSA Safer Practice Notice 14, Right Blood Right Patient (2006) which includes competency assessments for all staff involved within transfusion process.

Errors around patient identification occur when staff do not follow established protocols, resulting in no true check of the patient identity taking place. The final bedside check is recognised as a critical point in the transfusion chain and the last chance to detect errors including patient identification errors, hence SHOT recommended a patient education campaign entitled, “Do you know who I am?”.

### **Process**

It is normal practice in our organisation to log annual SHOT reports on the Quality Hospital Management software, and to raise non-conformances where recommendations require corrective actions locally. These are then discussed at the Hospital Transfusion Committee Meeting, before being raised to the Trust Clinical Governance and Risk Committee.

After the 2009 SHOT recommendations were discussed at the Hospital Transfusion Committee meeting in September 2010, limitations were noted for this recommendation that some patients may be unable to confirm their identity. For the majority of patients however it was agreed that the, “Do you know who I am?” campaign was relevant to their contact with the Trust. Examples of patient mis-identification could range from incorrect dinners being served to incorrect patients being X-Rayed, any of which could have a devastating effect upon the patient and their family. With this in mind the Transfusion Practitioner was asked to investigate how this particular recommendation could be moved forward and then report back for the December 2010 Hospital Transfusion Committee meeting.

## Implementation Plan

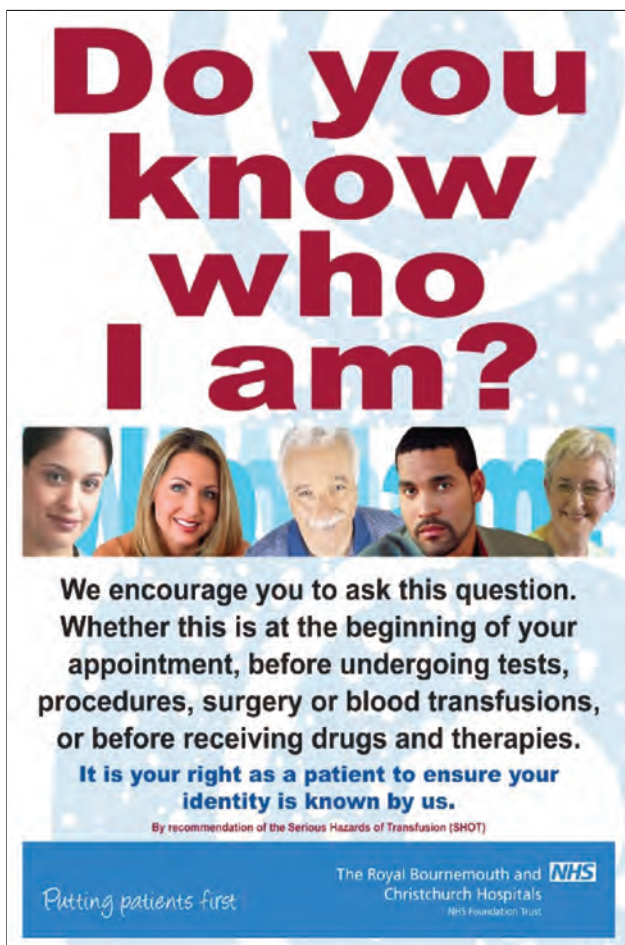
It was obvious that the success of this campaign would depend upon it being patient led; therefore the Transfusion Practitioner approached the Patient Advisory Liaison Service for assistance. They suggested two possible options:

Design a patient information leaflet with the recommendation clearly stated on it. This would inevitably occur a cost and distribution to patients might be difficult and ineffective given the amount of written information they were already presented with.

The other option was to contact the Communication department within the hospital and see if they were able to offer a simple intervention which patients would be able to readily access, and which would motivate patients to actively intervene in their treatment plans.

A Communication assistant was contacted on the 11th October 2010 and a copy of the SHOT report was sent highlighting the appropriate page, so that they could understand what the recommendation was.

The Communication department was keen to assist and together with the Transfusion Practitioner a poster was designed in keeping with corporate requirements and which was a simple and effective intervention which encompassed the question "Do you know who I am?"



Pictorially it was important that it included a range of ages and cultures so that a diverse patient group understood that it applied to all patients not just a few. It was also important to us that we included general appointments as well as interventions so that a culture of empowerment was developed.

The Transfusion Manager and Practitioner both agreed on the poster appearance and the Communication department produced the posters as shown.

The posters were circulated to all the patient information notice boards around both Trust sites, however the team was aware that patients are often distracted and worried when attending our premises – and do not always read written material on notice-boards.

The decision was made to transmit the poster image on the LED patient screens situated all around the trust, including Emergency Department, Outpatients, and Main Entrance. This allowed patients to view its contents whilst they awaited treatments and appointments – ensuring it was fresh in their mind when interventions commenced.

To ensure our staff were not surprised by patients questioning their ability to identify them the campaign poster was also included within the hospital Patient focus newsletter and in the staff newsletter "Buzz word".

Finally a short article was included in the local press to further publicise this campaign.

## Conclusion

To summarise, our Trust has actively managed the SHOT "Do you know who I am?" campaign. It is hoped that by implementing this campaign patients will feel more empowered to ask staff, "Do you know who I am?" before any procedure or intervention is carried out.

**Kim Locke**

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**Royal Bournemouth & Christchurch Hospital NHS Foundation Trust**

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**Julie Johnson**

**Transfusion Manager**

**Royal Bournemouth & Christchurch Hospital NHS Foundation Trust**

*Email: julie.johnson@rbch.nhs.uk*

## References

NPSA/2008/SPN14 (09 November 2006) Right Blood Right Patient

SHOT (2009) Annual Report Summary





## ERRATA

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AUTUMN 2011, ISSUE 34

Article – Safe and Dignified: The Donation Chair - page 8, 2nd paragraph

This read “Following consideration of a number of reasons (see below for more details), NHSBT’s clinical and operational view is now that donating in a seated position would have advantages over the current “traditional” *prone/semi prone* position.

This should read “traditional” *supine/semi supine* position.

Article – Common Inherited Disorders of Clotting: Part 2, page 15, 1st paragraph

This read ‘Inherited deficiencies of plasma proteins involved in blood coagulation generally lead to lifelong bleeding disorders, whose severity is *inversely proportional to the degree of factor deficiency*.

This should read *directly proportional to factor deficiency*.

Please let us know if the mailing address for your copy of Blood and Transplant Matters is not correct  
contact: [carol.griffin@nhsbt.nhs.uk](mailto:carol.griffin@nhsbt.nhs.uk)

## Next Edition

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**Issue 36 will feature articles on:**

- Learn Blood Transfusion – Elearning for Safe Transfusion
- Serious Adverse Blood Reactions and Events (SABRE) Reporting and the Role of the Principal Haemovigilance Specialist (PHS)
  - Transfusion-Induced Immunomodulation
  - The NHSBT/MRC Clinical Studies Unit
- Thromboelastography and Liver Transplantation
  - An Update on the NHS Cord Blood Bank
- An Update on the European Union Organ Donation Directive

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](mailto:derwood.pamphilon@nhsbt.nhs.uk)

### 1. Selection and Allocation of Solid Organs for Transplantation:

- a) The Human Tissue Authority has a statutory role in the selection of allocation policies for organs donated by deceased donors.
- b) Selection relates to who gets the donated organ.
- c) Families can ask for a directed allocation, of organs from a deceased donor, to a named individual on the national transplant list.
- d) The selection and allocation criteria are the same for all donated organs.

### 2. The National Scheme for Paired Living Kidney Donation:

- a) It is estimated that around one third of potential living donor transplants cannot proceed with a straightforward transplant because of ABO blood group incompatibility or human leukocyte antigen (HLA) sensitisation.
- b) Paired donations have been legally possible for over ten years.
- c) By the end of July 2011, less than 1% of living kidney donor transplants were made possible by this scheme.
- d) The first pairs were matched in 2009.

### 3. Since the Scheme Started:

- a) Less than 300 pairs have been registered.
- b) Over 200 transplants have been identified.
- c) Over 70% of the identified transplants proceed.
- d) All transplants have only involved a 2-way exchange.

### 4. Of the 108 Transplants to the end of July 2011, Performed Under the Scheme:

- a) 48 patients successfully received a transplant through the 2-way exchange.
- b) 48 patients successfully received a transplant through the 3-way exchange.
- c) 60 patients successfully received of transplant through the 3-way exchange.
- d) 0 patients successfully received a transplant through the 3-way exchange.

### 5. For Donor-Patient Pairs with a Blood Group Incompatibility:

- a) Donor O - recipient A with HLA incompatible pairs were matched in 20%.
- b) Donor B - recipient A were matched in 20%.
- c) Donor A - recipient B were matched in 29%.
- d) Donor A - recipient B were matched in 27%.

### 6. Transplantation For Diabetics:

- a) Renal transplantation has a poorer outcome in diabetics than in other patients with chronic renal failure (CRF).
- b) Diabetic patients with CRF have a better quality of life and life expectancy with dialysis than those with a renal transplant.
- c) Pancreas only transplantation has a higher long-term graft survival than a combined pancreas and kidney transplant.
- d) Combined pancreas and kidney transplants have only been performed in the last 10 years.

### 7. Islet Langerhans Cell Transplants:

- a) Are available at all transplant centres.
- b) Result in 5-year insulin independence rates of more than 50%.
- c) Result in many patients maintaining a functionally useful level of insulin production.
- d) Are associated with a high complication rate.

### 8. Ex-Vivo Lung Perfusion and its Implications for Pulmonary Transplantation (EVLP):

- a) Lung transplantation has a poor – less than 30% – long-term survival in young recipients.
- b) Only 15-20% of donors have lungs which currently can be used.
- c) EVLP cannot reinflate collapsed areas.
- d) EVLP is unlikely to increase the supply of suitable lungs for transplantation.

**9. Significance and Measurement of (Human Leukocyte Antigens) HLA and their Antibodies:**

**HLA**

- a) HLA is only found on Leukocytes.
- b) HLA is only involved with rejection of transplanted organs.
- c) HLA is highly genetically conserved.
- d) HLA is directly targeted by the immune system.

**10. HLA**

- a) All HLA is insoluble in plasma
- b) Some HLA can be absorbed onto red cells.
- c) Multiple red cell transfusion is not a risk in HLA sensitisation.
- d) Pregnancy is not a risk of HLA sensitisation.

**11. HLA**

- a) Immunosuppression is very successful in preventing rejection by pre-existing donor HLA-specific antibodies.
- b) Platelets are rich in HLA class II expression.
- c) Red cell transfusion reactions mediated by HLA specific antibodies are a major clinical problem.
- d) HLA antibodies directed against platelets can cause platelet refractoriness.

**12. HPA Selected Platelets:**

- a) Antibodies against human platelet antigens (HPA) causes neonatal alloimmune thrombocytopenia (NAIT).
- b) NAIT is commonly due to HPA-1a and HPA-5a antibodies together.
- c) NAIT is usually due to the HPA-5a antibody.
- d) Maternal IVIgG treatment during pregnancy is not a treatment option.

**13. Cold Auto Antibodies:**

- a) Cold agglutinin disease is not seen in children.
- b) Cold agglutinin disease is caused by pathologic cold-reacting auto antibodies – usually IgA.
- c) Secondary cold agglutinin disease can be due to mycoplasma infections.
- d) In primary cold agglutinin disease, the red cell antigen target is i.

**14. Extracorporeal Membrane Oxygenation (ECMO)**

- a) ECMO was first used in 2001.
- b) Adult ECMO is available in most DGH ITU's.
- c) Major haemorrhage is not a problem with ECMO.
- d) ECMO results in high usage of platelets.

**15. HIV Lookback Audit in England and Wales 1995 - 2009**

- a) Routine screening of blood donations for HIV began 20 years ago.
- b) During 14 years of surveillance, lookback identified/confirmed HIV transmission and measured HIV transmission through blood transfusion.
- c) HIV-NAT testing has not improved the detection of HIV positive.
- d) HIV lookback and its surveillance has now been discontinued.

*The CPD Section is a self-assessment exercise which allows readers to evaluate their understanding of each article. The answers are to be found within the articles themselves. Most CPD schemes allow this type of exercise to be eligible for credits as self-directed learning.*

# Diary Dates

## 2012

**9-10 February 2012**

**ESH Updates in Clinical Hematology**

Location: Paris, France

For more information contact: [www.esh.org](http://www.esh.org)

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**15 February 2012**

**Targeted Treatments for Haematological Cancers**

Location: The Education and Conference Centre, Stewart's Grove, SW3 6JJ (The Royal Marsden NHS Foundation Trust)

For more information contact:

[www.royalmarsden.nhs.uk/studydays](http://www.royalmarsden.nhs.uk/studydays)

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**1-4 April 2012**

**38th EBMT Annual Meeting 2012**

Location: Geneva, Switzerland

For more information contact: [www.ebmt.org](http://www.ebmt.org)

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**12-13 April 2012**

**13th Annual NATA Symposium**

Location: Tivoli Hotel & Congress Center, Copenhagen, Denmark

For more information contact:

[www.nataonline.com](http://www.nataonline.com)

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**16-18 April 2012**

**BSH 52nd Annual Scientific Meeting**

Location: SECC, Glasgow

For more information contact:

[sarah.lapsley@bshconferences.co.uk](mailto:sarah.lapsley@bshconferences.co.uk)

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**20 April 2012**

**4th International StKB Future Workshop on Hemo and Cell Therapy**

Location: University Medical Center, Johannes Gutenberg University, Mainz, Germany

For more information contact: [hitzler@uni.mainz.de](mailto:hitzler@uni.mainz.de)

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**20-22 April 2012**

**ESH-EHA Scientific Workshop on Mesenchymal Stem Cells**

Location: Mandelieu, France

For more information contact: [www.esh.org](http://www.esh.org)

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**22-25 April 2012**

**ESH-EBMT Training Course on Haemopoietic Stem Cell Transplantation**

Location: Sofia, Bulgaria

For more information contact: [www.esh.org](http://www.esh.org)

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**23-24 April 2012**

**Introduction to Immunology**

Location: University of Warwick, Coventry, UK

For enquiries and an application form, please email Dr Steve Hicks, University of Warwick:

[s.j.hicks@warwick.ac.uk](mailto:s.j.hicks@warwick.ac.uk)

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**25-28 April 2012**

**XXXIV World Congress International Society of Hematology**

Location: Cancun, Mexico

For more information contact:

[www.hematology2012.com](http://www.hematology2012.com)

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**10-13 May 2012**

**XIIth European Symposium on Platelet and Granulocyte Immunobiology**

Location: Warsaw, Poland

For more information contact: [www.espgi2012.pl](http://www.espgi2012.pl)

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**23-24 May 2012**

**IPFA/PEI 19th International Workshop on Surveillance and Screening of Blood Borne Pathogens**

Location: Budapest, Hungary

For more information contact: [www.ipfa.nl](http://www.ipfa.nl)

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**4-8 June 2012**

**Africa Society for Blood Transfusion, 6th AfSBT Blood Transfusion Congress including ISBT Academy Education Day – Training and Quality Lead to Safe and Sustainable Blood Services**

Location: Mauritius

For more information contact either:

[janaki.sonoo@gmail.com](mailto:janaki.sonoo@gmail.com) or

[Beryl.Armstrong@nbisa.org.za](mailto:Beryl.Armstrong@nbisa.org.za)

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**14-15 June 2012**

**Current Issues in Transfusion Medicine and Blood Donation. Collection, Processing and Usage of Blood and Blood Products**

Location: Riga, Latvia

For more information contact: [www.isbtweb.org](http://www.isbtweb.org)

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**7-12 July 2012**

**32nd International Congress of the ISBT**

Location: Cancun, Mexico

For more information contact: [www.isbtweb.org](http://www.isbtweb.org)

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**23-26 August 2012**

**ISEH – Society for Hematology and Stem Cells  
41st Annual Scientific Meeting**

Location: Hotel Okura, Amsterdam, Netherlands

For more information contact: [www.iseh.org](http://www.iseh.org)

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**19-21 September 2012**

**Current Issues in Transfusion Medicine and Blood Donation. Collection, Processing and Usage of Blood and Blood Products**

Location: Kiev, Ukraine

For more information contact: [www.isbtweb.org](http://www.isbtweb.org)

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**6-9 October 2012**

**AABB Annual Meeting & CTTXPO**

Location: Boston Convention Center, USA

For more information contact: [www.aabb.org](http://www.aabb.org)

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**8-11 December 2012**

**2012 ASH 54th Annual Meeting and Exposition**

Location: Georgia World Congress Center in Atlanta, USA

For more information contact: [www.hematology.org](http://www.hematology.org)

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**10-14 December 2012**

**2nd International Conference on Blood Safety and Safety Surveillance**

Location: Abidjan, Ivory Coast

For more information contact: [www.cistha.com](http://www.cistha.com)

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