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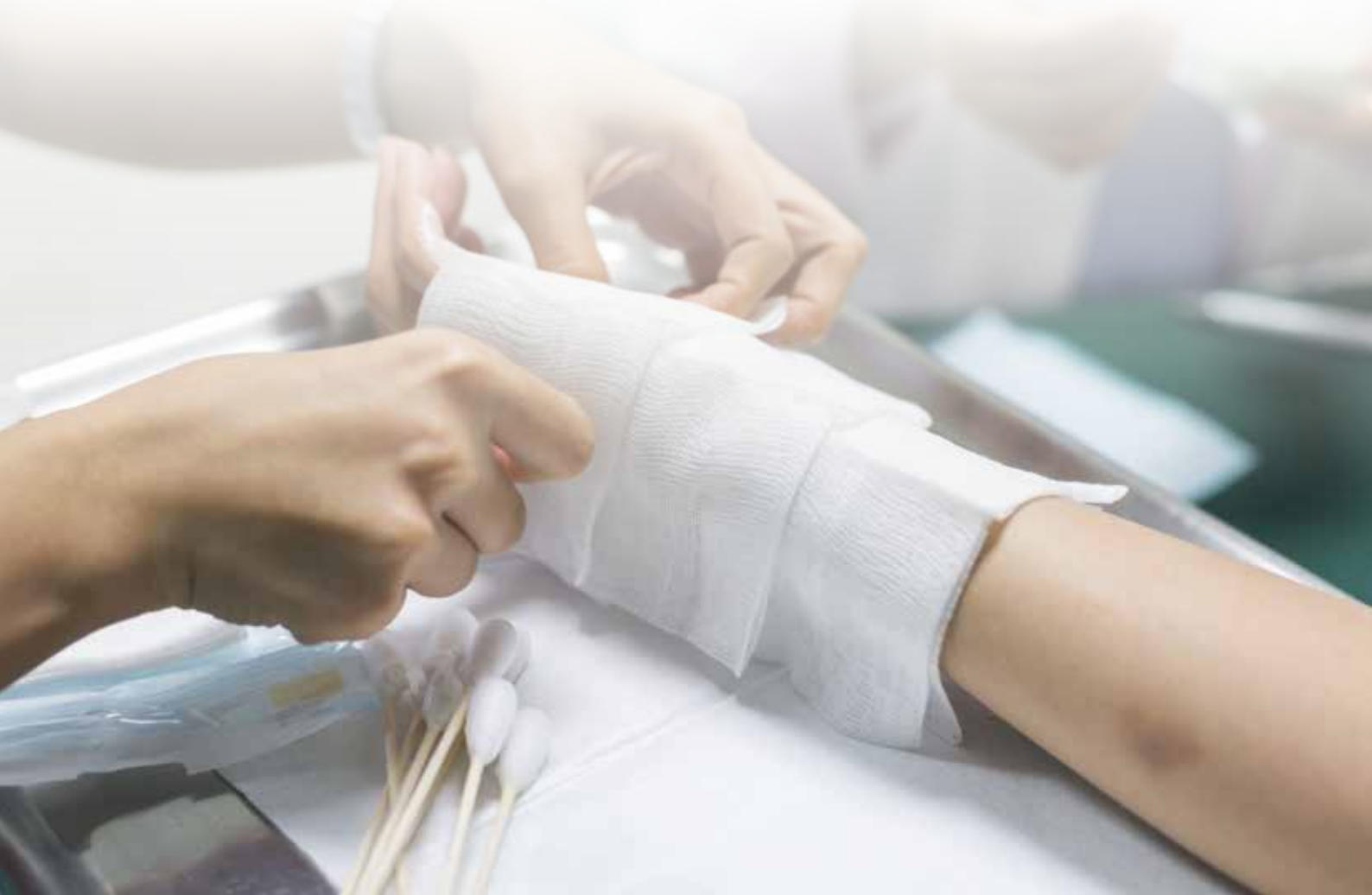
NHS
Blood and Transplant

Blood and Transplant Matters

Information for hospitals served by NHS Blood and Transplant

Inside



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Next Edition

Issue 52 will feature articles on:

- The importance of Engaging Nursing and Medical Students in Promoting Organ Donation.
- Out of Hours Blood Transfusion Audit.
- John Forsythe Associate Medical Director for ODT Interview.
- Organ Donation Memorials.

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

EDITORIAL

Welcome to Edition 51 of Blood and Transplant Matters and I hope you enjoyed the last edition and found areas of interest or use.

This edition starts with Catherine Spoors discussing the blood loss due to burns and provides an insight to the red cell requirement of burns patients at various stages of treatment. Catherine also, outlines the requirement of other blood components, use of monitoring and use of crystalloid and colloid solutions.

Therese Callaghan next presents results of a recent Audit of Weekday Out of Hour's Referral for Urgent Therapeutic Apheresis Procedures during January to December 2015. Most of the referrals met audit standards, however, some did not. As a result, the Therapeutic Apheresis on call manual has been amended.

There follows next, a series of articles looking at different aspects of organ donation and transplantation. Dale Gardiner looks at the actual wording used by medical staff to discuss the fact that a patient (their loved one) suffered brain death, in such a way as to promote likely positive consent for deceased organ donation. Food for thought! Once an organ has been offered, it must be appropriately allocated to a patient.

Diana Wu and Gabriel Oniscu describe a large, multi-centre study, looking at access to and outcomes from renal transplantation, including survival, patient reported outcome measures, cost-effectiveness and alternative organ allocation schemes within the ATTOM Study.

This should provide valuable and high quality research in order to tackle current issues and positively influence policies and care for renal patients in the UK. More UK deceased donors are now over 60 years old and Gavin Pettigrew outlined a trial looking at the use of urgent kidney biopsy to identify age-related damage and whether that will aid selection of kidneys from older donors that would offer acceptable transplant outcomes. This it the PITHIA Trial – some ancient history and mythology is provided free of charge! Next Lisa Burnapp describes the role of Non-Directed Donation in Living Donor Kidney Transplantation. Almost half of all organ donors are living donors, but less than 10% of all living kidney donors are Non-Direct Altruistic Donors (NOAD) in the UK. Lisa describes the background of how NOAD is a part of Living Donor Kidney Transplantation (LDKT) 2020 and another strand used to increase renal transplantation in the UK.

Still with organ donation, but a switch from the kidney to the whole hand. Gordon Crowe describes, along with a short history of hand and upper limb Vascularised Composite Transplantation, the planning and approach take for the UK's first double hand transplant.

As usual, there is a Patient's Story, which continues to remind us all, why all the work is so necessary.

Finally, but not least, Chris Philips and Tracey Scholes describes the results of this years Customer Satisfaction Survey, which is one way the NHSBT, informs improvements.

As always, there are both CPD questions based upon these articles, with answers appearing in the next edition – and some interesting cases with suggested answers and some references, which I hope are both interesting and informative.

Have a happy read. All good points are due to the authors, any mistakes are mine. Any comments should be sent to myself or my hard working Editorial Assistant Lynne Hodkin at blood&transplantmatters@nhsbt.nhs.uk.

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Blood and Fire: Bleeding and Transfusion in Major Burns

Major burns are inevitably associated with blood loss, and the hospital blood bank is a key resource in their treatment. The transfusion requirements of burns patients are determined by the size and depth of the burn. Patients may also suffer non-burn haemorrhage, for example, from injuries sustained during an explosion. Post-burn anaemia is multifactorial, and blood loss occurs at various time points during the initial injury and subsequent hospital admission.

Immediate Blood Loss

At the point of injury, red cells within burned tissues are destroyed. Red cells are also sequestered into thromboses within the microcirculation of the injury and, to a variable degree, surrounding tissue. In full-thickness burns of more than 10% Total Body Surface Area (TBSA), it has been estimated that red cell losses can be calculated at 10% + 2% for every 10% full-thickness loss above 10% - in other words in a 40% TBSA full-thickness burn, losses of 16% of red cells can be expected within the first six hours (Topley, Jackson *et al.* 1962). Escharotomy (surgical release of the inelastic, leathery burned tissue to alleviate pressure effects on progressively swelling limbs or torso), may be required in the early phase of resuscitation, and can result in significant additional losses. In the absence of surgical or traumatic bleeding however, acellular fluid losses outstrip red cell losses in the immediate phase, and early resuscitation predominantly utilises synthetic crystalloid and colloid solutions.

Early Blood Loss

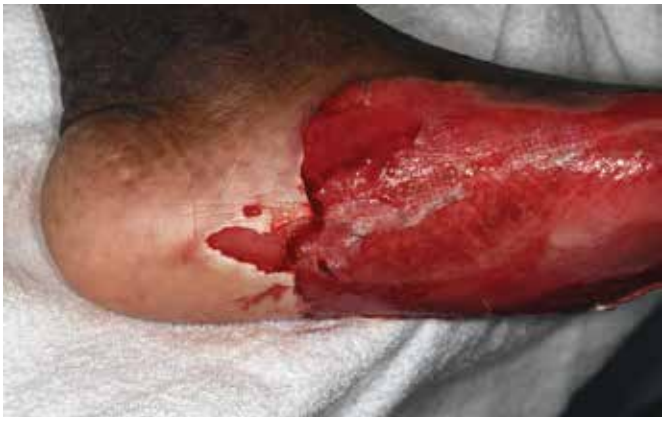
One of the mainstays of burns care is early surgical debridement. Burned tissue is a potent driver for the systemic inflammatory response which, if left unchecked, can overwhelm the patient. Excision of large burns is usually carried out within the first 48-72 hours post-injury, and this approach has improved mortality in burn care. Blood loss during these operations is inevitable and on occasion can rapidly amount to massive haemorrhage. Formulae exist to estimate the expected bleeding from burn excision (figure 1), although there is considerable inter-individual variability. Near-patient intraoperative monitoring of haemoglobin is invaluable in allowing the judicious use of red cells and avoiding over-resuscitation in a rapidly-changing situation. Point-of-care coagulation testing is less well-established in burns anaesthesia as it is in other specialties, and viscoelastic clotting assays are currently reserved for research use in burns practice. As such, the approach to the use of blood products remains empirical, with major haemorrhage protocols being used to deliver a ratio of red cells, plasma, platelets and other blood products to support effective coagulation during rapid bleeding.

The surgical technique itself influences bleeding: with tangential excision or "shaving" procedures, diffuse ooze from the wound bed can be significant. Fascial excision (removal of burn eschar and subcutaneous tissue to the depth of muscle fascia) is less commonly performed as it results in removal of healthy tissue and leaves contour deformities, though haemostasis is improved. One important factor in predicting surgical blood loss is the presence of infection: bleeding from the excision of infected eschar can be expected to be approximately double that of an uncomplicated burn (Desai, Herndon *et al.* 1990). Harvesting of skin from donor sites is another potential source of loss, and it can in some situations equal the original burn wound area.

Various blood-sparing techniques are employed during burn debridement. The use of tranexamic acid, maintenance of normothermia, electrocautery, topical application of thrombin and/or vasopressors such as phenylephrine or epinephrine, tumescent subdermal/subeschar injection of adrenaline solutions, expedited surgery with multiple personnel working in tandem, and staged procedures (for example, delaying graft harvest) all mitigate against the ineluctable bleeding. Tourniquets can be applied for the treatment of distal limb burns. The diffuse trickle seen in burn surgery unfortunately does not lend itself to cell salvage techniques.

Late Blood Loss and other Derangements

Despite the obvious and dramatic blood loss involved in burns surgery, the majority of administered blood products are, in fact, administered on the Burns Intensive Therapy Unit (ITU) by way of supportive care. In step with the intensive care world at large, restrictive Hb thresholds of 70 g/L have been found to be safe and well-tolerated in burns patients - and possibly associated with better outcomes compared with historical controls (Kwan, Gomez *et al.* 2006). Ongoing losses occur over the course of the ITU stay: repeated surgical procedures, dressing changes, blood sampling, vascular access and haemofiltration, and other complications of large burns such as acute gastric erosions (Curling's Ulcers) are all potential sources of late bleeding.



Repeated dressing changes to burn wounds may provoke considerable blood loss over the course of an ITU stay.

The bone marrow response to erythropoietin appears to be impaired after a major burn, despite elevated levels of erythropoietin in many patients. Infective and/or sepsis episodes during a prolonged burn ITU stay are almost universal, often recurrent, and can be severe. Derangements in platelet count and coagulation are common, and are treated in line with nationally recommended transfusion thresholds. Conversely, thrombocythemia, hypercoagulability and thrombosis are common during the later phases of burn injury, and thromboprophylaxis is vital. As well as common risk factors, inhalational injury, burn size, admission to ITU and number of surgical episodes are all associated with an increased risk of thrombosis in the burns population (Pannucci, Osborne *et al.* 2011).

The management of burn patients has improved over the last half century or so, such that injuries previously deemed unsurvivable are now treated with curative intent (Roberts, Lloyd *et al.* 2012). Transfusion requirements in extensive burn injury can be massive. The expertise of the transfusion service is crucial in caring for these patients.

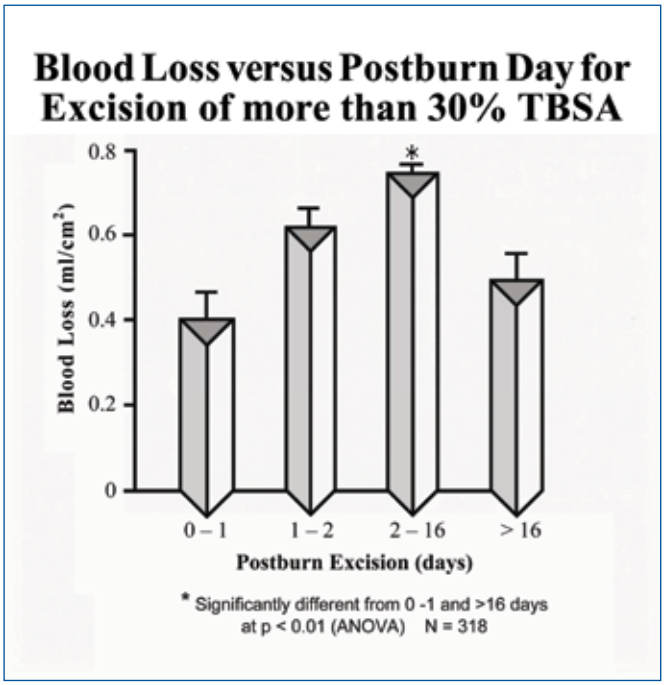


Figure 1. From: Desai, M. H., *et al* (1990). Early burn wound excision significantly reduces blood loss. Ann Surg, **211**(6), 753-759.

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Audit of Weekday Out of Hours Referral for Urgent Therapeutic Apheresis Procedures January – December 2015

Background

NHS Blood and Transplant (NHSBT) Therapeutic Apheresis Services (TAS) provides a range of Therapeutic Apheresis Procedures including Plasma Exchange, Red Cell Exchange and Leucodepletion.

Prior to January 2015, acceptance of overnight out of hours (17.00 – 09.00) referrals for urgent treatment was restricted to weekends (Friday-Sunday) and Bank Holidays.

On 01 January 2015, NHSBT TAS introduced 24/7 out of hours service for patients requiring urgent treatment which could not wait till the following day. It was agreed that the new service would be reviewed after one year to assess the impact on workload and to check that the additional cases accepted out of hours during the week were clinically justified.

Acceptance criteria are listed in the TAS on call manual SPN313 which references the American Society for Apheresis (ASFA) Guidelines; the ASFA guidelines list the possible indications for Therapeutic Apheresis (TA) and categorise as I-IV according to the role of TA in treatment of the condition (category I – TA accepted as first line treatment; category II – TA accepted as second line treatment; category III – role of TA not established; category IV – TA ineffective or harmful).

At the time of the audit period, the current guidelines were those published in 2013.

Method

TAS staff in each Unit were asked to collect data on all cases referred for treatment out of hours overnight.

The reason for referral for each case was assessed against the acceptance criteria as defined in the audit standard. The results were circulated among the TAS consultant group with a request to feedback opinion on the appropriateness or otherwise of cases which did not fall into one of the diagnostic categories 1-3 as set out below.

Audit Standard

The audit standard was that all out of hours overnight referrals should fall into one of the diagnostic categories listed in SPN313/6.1 Therapeutic Apheresis – On Call Manual section 8.4, viz.

1. Leucocytosis: with rapidly rising white cell count (WCC) with significant symptoms of hyperleucostasis.
   a. Acute myeloid leukaemia (AML) WCC more than 100.
   b. Acute lymphoblastic leukaemia (ALL) WCC more than 400.
   c. Chronic myeloid leukaemia (CML) WCC more than 200.
2. Thrombotic thrombocytopenic purpura (TTP).
3. Sickle cell crisis: acute chest, severe painful crisis, priapism, stroke, retinal infarction, hepatopathy.
4. Conditions outside the above list but considered individually on their own merits to require overnight treatment at the discretion of the NHSBT consultant.

Cases falling into categories 1-3 ('standard criteria') were regarded as by definition meeting the audit standard; cases falling into category 4 required further assessment to confirm that overnight treatment was required.

Results

A total of 50 cases were confirmed to have been referred for an urgent overnight weekday procedure. Of the 50 cases, 33 (66%) clearly met the audit standard by falling into disease category 1, 2 or 3. The breakdown was as follows: TTP (19), symptomatic hyperleucocytosis (9) and sickle cell crisis (5).

Four TAS consultants offered an opinion on some or all of the remaining 17 cases which did not meet the standard criteria.

Of these seventeen, 11 were assessed as indeed clinically justified, giving a total of 44/50 (88%). The diagnoses for these cases were as follows: renal vasculitis with diffuse alveolar haemorrhage (DAH) (n=3), atypical haemolytic uraemic syndrome (aHUS) (n=2), symptomatic hyperviscosity with severe symptoms (n=2), hyperviscosity but no information on symptoms (n=1), systemic lupus erythematosis (SLE) with DAH (n=1), myaesthenia gravis with bulbar involvement but not in Intensive Therapy Unit (ITU) (n=1) and methemoglobinaemia (n=1).

Of the remaining six, five were considered not to be clinically justified (10% of the total), while one case could not be assessed due to insufficient information about the patient's clinical condition. The diagnoses in these six cases were as follows: anti-GBM vasculitis - dialysis dependent and without DAH (n=2), Guillain-Barre syndrome unresponsive to Intravenous immunoglobulin (IVIg) (n=1), anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (n=1) and HUS (n=1). The patient who was deemed as unassessable had a diagnosis of rapidly progressive glomerulonephritis (RPGN) but no information on subtype or presence or otherwise of DAH.

Discussion

The majority of cases (88%) were deemed clinically justified although only 33 (66%) fell into disease category 1, 2 or 3.

For those 11 cases which did not fall into category 1,2 or 3 but were assessed overall as clinically justified, there was uniform agreement among the assessing consultants that overnight treatment was clinically justified for certain conditions, namely hyperviscosity with severe symptoms and renal vasculitis /SLE with associated DAH. These formed a relatively high proportion of the cases (6/11). Other cases were either extremely rare (for example methemoglobinaemia) or there was less consensus.

For cases deemed not to be clinically justified, there was unanimity among the three consultants regarding one case (NMDA encephalitis). For the other cases, only a maximum of two consultants offered an opinion but were mainly in agreement.

Since this review was undertaken the ASFA guidelines have been updated and the new version published in July 2016.

Audit Recommendations

1. Update the TAS on call manual to include additional diagnostic categories where there is general consensus that overnight treatment is or may be clinically justified.
2. Extend analysis of data to include identification of authorising consultant as TAS or non-TAS consultant and assess if there is any difference in decision-making between the two groups.
3. Discuss with TAS consultants a mechanism for capturing and collating out of hours referrals which are not accepted for overnight treatment.
4. Review assessments against new ASFA guidelines.
5. Circulate report to all NHSBT patient facing consultants.
6. Present final report at biannual NHSBT patient-facing consultants meeting.
7. Submit report for publication.
8. Undertake extended audit to include all out of hours referrals.

An audit of all out of hours procedures is now in the planning stages.

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Explaining Death Confirmed Using Neurological Criteria to Families

In 2013, in preparation for the launch of the new National Deceased Donation Simulation Course for Intensive Care Trainees, I emailed many colleagues in the UK to see if they were aware of any documents to help guide intensive care doctors in how to explain 'brain death' to families. Surprisingly, very little has been done in this area.

While there is research evidence to support the belief that explaining 'brain death' well to families, and at a pace commensurate with their emotional needs, is positively associated with consent for deceased organ donation, the exact words to use remain quite opaque.[1] This is not to say good work has not occurred in this area. It is for example becoming increasingly common for clinicians to offer families the chance to witness the second set of brainstem tests as this is felt to be beneficial for their understanding and acceptance of the tragic reality of their loss.[2]

There is no official validation or research for the below but it does reflect how I conceptually understand death determined by using neurological criteria and how I approach communicating this to the families of patients under my care. I would welcome your feedback.

Essential Messages

- Death is suspected
- Tests to confirm death

The essential messages I try to communicate is that death is suspected to have already occurred and that tests are required to confirm or refute this suspicion.

Key points I like to communicate are:

1. The brain injury is so severe that death is suspected to have already occurred.
2. There is a plan to carry out a set of tests to see if the patient will ever regain any consciousness or ever breathe again.
3. The tests will be done carefully by two senior doctors.
4. If the tests confirm that these essential brain functions are permanently lost; this will mean the patient has died.
5. The tests will not hurt the patient.
6. The tests will be done at the bedside by examining the patient and as part of the tests the patient will be removed from the mechanical ventilator to see if the patient can breathe.

7. The tests will be done twice.
8. There is an opportunity for family to observe the second set of tests if desired.
9. If the tests do not show the presence of any of the essential brain functions, it will confirm that the patient has died.

It is vital that family reaction and understanding is assessed as the information is relayed and working with my bedside nurse and specialist nurse for organ donation we always try to pace the delivery according to the family's needs. If there are points of confusion or distress, or the information is too overwhelming, then further explanation or time is given before proceeding.

Accepting that individual styles may vary (even when I am doing the speaking) and regurgitating quotes of any text would appear forced and unnatural, I offer as way as illustrative example the below paragraph. The imagined case is for Margaret a middle-aged woman who had an overwhelming subarachnoid haemorrhage, who is in intensive care awaiting testing to determine death using neurological criteria.

"As you know Margaret has had a very bad bleed in her brain. As you saw, she lost consciousness almost immediately and the paramedics had to put the breathing tube in because she was no longer breathing for herself. Since coming to hospital we have not seen her breathe and many of her brain functions appear to have ceased.

"The scan of her brain is very abnormal and devastating. My fear is that the damage Margaret has sustained to her brain, is so severe, that she may have already died.

"Another senior doctor and I are planning to carry out some tests on Margaret to see if she will ever regain any consciousness or ever breathe again. If the tests confirm that these essential brain functions are permanently lost, this will confirm to us, that she has died.

"The tests won't hurt Margaret. One of these tests will be to shine a light in her eyes to see if her pupil gets smaller, much as the nurses have already been doing in the Intensive Care Unit. We will also take her off the ventilator to see if she can breathe by herself.

"The tests will be done twice. We'll do the first set of tests shortly but we'll give you the chance to watch the second set of tests if you wish. Some families find this helpful, to see for themselves.

"I'm very sorry; but I expect the tests will confirm that Margaret has already died."

Brain Death or Brainstem Death or just Death?

It might appear strange to the reader that in the above example I did not use the term 'brain death' or 'brainstem death' even once. I find these terms confusing and unhelpful. The term brain death is loosely used by the media, often conflating persisting coma with brain death. Neurologists in the USA have also been shown to have an inconsistent rationale for accepting 'brain death' as death.[3] Is it any wonder then that a public survey carried out in 2013 in Northern Ireland found that nearly 50% of those surveyed thought that maybe you could, or didn't know if you could, recover from brain death.[4]

More compelling to me is that nearly a decade ago the Academy of Medical Royal Colleges (AoMRC) Code of Practice (2008) for the Diagnosis and Confirmation of Death abandoned the terms and instead refers to the 'Diagnosis and Confirmation of Death in a Patient in Coma.'[5]

'Brain death' and 'brainstem death' are terms that are therefore poorly defined, widely misunderstood, difficult to explain and abandoned by the authority who gives us our Code of Practice in the UK for confirming death. The time has surely come for health professionals to withdraw the term brain death from their lexicon and allow it to historically die; especially when we are explaining how we know someone has died to families.

Actors representing family from the Nottingham Deceased Donation Simulation Course.

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The ATTOM Study

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Introduction

The Access to Transplantation and Transplant Outcomes Measures (ATTOM) study is a National Collaborative Research Programme funded by the National Institute for Health Research (NIHR). The programme was launched in 2011, with the overarching aims of improving equity in access to renal transplantation and maximising the benefit and cost-effectiveness of renal transplantation in the UK. ATTOM is the first and largest study of its kind, having recruited around 7000 dialysis, waiting list and transplant patients from all UK renal units as part of a truly national prospective cohort study. The interdisciplinary and collaborative approach of the ATTOM study has enabled implementation of a high quality and relevant research programme, putting the UK at the international forefront of clinical research in transplantation.

Importance of the Study

Kidney transplantation is widely regarded as the best treatment for end-stage renal disease (ESRD). When compared with dialysis, transplantation leads to a two- to three-fold increase in life expectancy and, it is often believed a better quality of life. However, while the success of transplantation has led to an exponential rise in demand, there has not been a corresponding increase in the availability of donor organs. This has led to increasing challenges in access to and allocation of this scarce resource. Furthermore, the changing demography of patients with ESRD with an older population and more significant comorbidity, has added further complexity to treatment decisions at an individual patient as well as societal level. It is currently unclear what constitutes best practice with regards to appropriate and equitable

access to renal transplantation. This is reflected in the wide variation of outcomes of ESRD patients across UK centres. In the ATTOM study a comprehensive analysis of patient and centre specific factors that influence access to and outcomes from renal transplantation, including clinical outcomes, patient reported outcomes (Gibbons, *et al.* 2017) and cost-effectiveness (Li, *et al.* 2015) is being undertaken. The evidence base will be used to identify and define best practice, reduce inter-centre variability and improve outcomes across all UK centres through the development of a more equitable and validated approach to transplant listing and organ allocation (Li, *et al.* 2016). These aims are in line with the commitment of the NHS to reducing variation in the quality and delivery of medical care across the UK.

Research Plan

The research programme is divided into five main work streams:

1. Access to transplantation.
2. Survival on dialysis and after transplantation.
3. Patient reported outcome measures including quality of life.
4. Health economic analysis.
5. Development of alternative organ allocation schemes bringing together work from the previous workstreams.

The detailed methods and study protocol are published (Oniscu, *et al.* 2016). Extensive data were collected prospectively by trained research nurses based in each of the UK centres. Collaboration with the UK Renal Registry and NHS Blood and Transplant allowed this large amount of data to be held and managed securely through established systems. A variety of research techniques were employed including both quantitative and qualitative analysis, in order to gain an in-depth insight into individual centre practices, outcomes and beliefs of both patients and healthcare professionals (Calestani, *et al.* 2014). The study was designed by an interdisciplinary consortium of key stakeholders enabling the identification and planning of research outputs crucial and relevant to the improvement of current renal transplant services. One of the major outputs of the ATTOM study will be a novel survival prediction tool for patients with ESRD. This tool will be available as a mobile or web-based platform enabling clinicians to input various risk factors, and will provide an individual prediction of outcomes at different time points for different treatment modalities. This tool will facilitate informed and evidence-based treatment decisions and discussions with patients, and could also be used to inform a nationally agreed listing threshold, in order to standardise access to the transplant waiting list. Another key translational aspect of the study will be the development of an alternative kidney allocation scheme. This will explore the balance of cost, survival benefit, quality of life gains and patient acceptability, in order to maximise the benefit to society from donor kidneys.

Conclusions

The delivery of renal transplant services currently faces several major challenges. The ATTOM study is an excellent example of clinicians, patients, academics, registries, NHSBT and other members of the renal transplant community coming together to provide valuable and high quality research in order to tackle current issues and positively influence policies and care for renal patients in the UK. On behalf of the lead investigators the authors sincerely thank all patients and renal centres for their involvement in the study.

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An Evaluation of a Pre-Implantation Renal Histopathology Service, at the time of Organ Donation: The PITHIA Trial

Ancient History

In 457 BC. the great Lydian Emperor Croesus (the first producer of standardised gold coins) sent word to the Pythia, the Oracle at the temple of Apollo, before his planned attack on the Persian Army of Cyrus the Great. The Pythia existed from the 8th Century BC to around 390 AD and were the most famous soothsayers of the ancient world. Croesus was told that if he attacked the Persians, then a great empire would be destroyed. Accordingly, he launched his campaign, only to discover that the great empire destroyed was in fact his own – the Lydians were comprehensively destroyed and Croesus condemned to burning. His legacy is a reminder of the hazards of relying on unsubstantiated tools that offer to predict the future.

The Oracle in Transplantation

There is a great shortage of kidneys for transplantation with over 5000 people currently on the waiting list, and a median waiting time for a transplant of three years. All kidneys from deceased donors carry risk to the recipient (risk of not working, or of disease transmission), but donor age is strongly associated with poor function and early failure of the kidney transplant. For patients in whom kidneys fail to work at all, the consequences can be devastating, with an average one-year mortality of 25%. However, the majority of potential UK deceased donors are now over 60 years old, and better use of kidneys from these donors would be expected to reduce waiting times, and to improve survival for kidney patients. Thus, if we can more accurately identify kidneys from older donors that are better 'quality', we can maximize numbers of transplants performed without compromising transplant outcomes.

The use of urgent kidney biopsy to identify age-related damage has been reported to aid selection of those kidneys from older donors that would offer acceptable transplant outcomes. This approach has not been widely adopted in the UK, because the exact impact that the extra information provided by biopsy has on transplant numbers and on transplant outcomes is not clear, and its cost effectiveness remains unproven. The PITHIA trial (Pre-Implantation Trial of Histopathology in Renal Transplant Allografts) aims to evaluate whether pre-implantation biopsies can increase the number and quality of kidneys for transplantation.

The Randomised Registry Trial

Patient registries have become an important part of clinical practice throughout many branches of medicine and have provided a valuable source of data for quality assurance and research (typically for large cohort studies). A further innovation has been the development of the

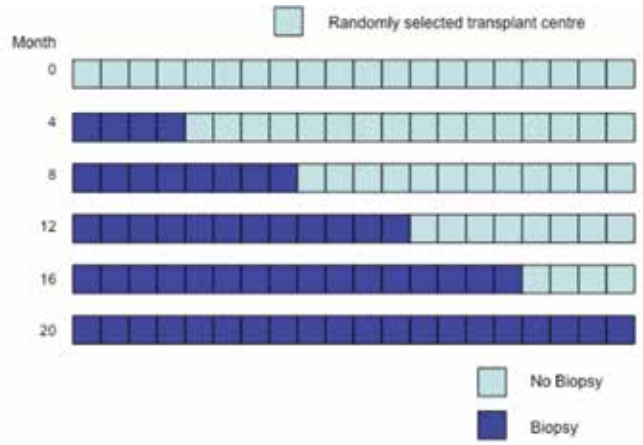
randomised registry trial, in which patients are followed up after randomisation and intervention using only follow-up data that is already routinely collected on the registry. This efficient way of collecting information is substantially less onerous for patients and clinicians and can markedly reduce costs as well as increasing recruitment to the trial.

NHS Blood and Transplant (NHSBT) holds the national transplant registry for the UK and it is widely regarded as one of the most comprehensive and high quality registries in transplantation. The PITHIA trial will be a randomised registry trial, using the NHSBT UK transplant registry, and will be the first of its kind in transplantation.

The PITHIA Trial

The PITHIA trial aims to test whether having access to pre-implantation kidney transplant biopsies will increase the number of deceased-donor kidneys for transplantation and/or increase the quality of those kidneys. It is a stepped-wedge cluster randomised trial that will evaluate the introduction of the new National Histopathology Service. Kidney biopsies will be taken by the National Organ Retrieval Service (NORS) teams at the time of organ recovery, before being prepared, stained and scanned by a biomedical scientist at the NORS team base.

Figure 2 Cluster, randomised, stepped-wedge clinical trial



The images will be sent electronically to one of a group of specialist renal pathologists who will provide a score of underlying renal disease/injury (using the Remuzzi scoring system) for the implanting clinicians. The clinicians and potential recipients can then use this additional information to help decide whether to use the kidney or not. The participating transplant centres will gain access to the histopathology service in a stepped fashion, with the order determined randomly (see figure 2). This trial design will enable comparison of outcomes before and after the histopathology service becomes available.

The Future

The PITHIA trial will demonstrate the value of a national, immediate histopathology service in transplantation. In addition to refining and developing the tools to evaluate organ quality, there is the capacity to expand the service to help exclude malignancy from deceased donor organs, and help evaluate other organs for transplantation. We anticipate that randomized-registry trials that use the NHSBT dataset will become the routine approach to UK transplant trials in future. http://www.pithia.org.uk

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Shifting Paradigms: The Contribution of Non-Directed Donation in Living Donor Kidney Transplantation

Background

In common with many other countries, living organ donation in the UK is well established, based upon excellent patient and transplant outcomes and careful consideration of donor risk. The statistics speak for themselves: every year, 1100 people are transplanted from a living organ donor across the UK, most of whom are close family or friends. Almost half of all donors (44%) are living donors, with 97% donating a kidney and 3% a lobe of liver. One third of all kidney transplants are from living donors, providing expansion of the donor pool, more kidneys available for transplant and improved access to transplantation for all patients.[1,2] Transplantation makes economic sense, saving approximately £25,000 per year / per patient after the first year in comparison with the cost of dialysis. By avoiding the need for dialysis, pre-emptive transplantation is the treatment of choice for patients with end stage kidney disease (ESKD) and their families. A planned living donor kidney transplant makes this choice a reality and maximises the number of dialysis free years they can hope to enjoy.[3]

The nature and profile of living donor kidney transplantation (LDKT) has changed dramatically in the past twenty years. As clinical expertise and professional and patient confidence in the programme have grown, so has the immunological and clinical complexity of donors and recipients; LDKT offers options for these patients who may otherwise not be considered for transplantation. Change has been rapid and LDKT has been at the forefront of innovation and research.

Strategic Thinking

The UK Strategy *'Living Donor Kidney Transplantation 2020' (LDKT 2020)*[4] aims to maximise LDKT activity, transplant quality and patient benefit through expansion of the living donor pool. Protection of the living donor and 'state of the art' donor care is at the core of the strategy. It is an ambitious plan that sits alongside the deceased donation strategy *'Taking Organ Transplantation to 2020'*[5] and promises to deliver 1700 living donor transplants (26 per million population) by March 2020. Key to success is engagement with the wider transplant community- patients, professionals, commissioners - and all sectors of society.

Non-Directed altruistic donation, where a living person donates anonymously to someone in need of a transplant whom they do not know or have never met, has demanded a shift in thinking and approach. When it was made permissible in the UK under the Human Tissue Act in 2006, there was a low expectation that people would volunteer to donate outside their family or friendship groups. Yet, within under a decade, more than 500 people had done exactly that. Donating a kidney to a stranger is an exceptional act of generosity but it is increasingly accepted as the norm, with Non-Directed Altruistic Donors (NDADs) representing 8% of all living kidney donors in the UK. It is not for everyone and, even when interest is triggered by a personal life event or media story, it may take several months for people to step forward.

However, despite local and national publicity, many people remain unaware that they can donate an organ anonymously as a living person, so the focus is on raising awareness to ensure that everyone, across all sectors of society, knows that this might be an option for them should they wish to consider it. Although non-directed donation currently accounts for a relatively small proportion of the overall programme, it is a potential 'game-changer', particularly for patients who are likely to wait longer for a kidney - the immunologically or clinically complex recipients and those from black, Asian and ethnic minority communities.[1,2]

There are two ways in which a NDAD can donate: either into the UK Living Donor Kidney Sharing Schemes (UKLKSS) to create an altruistic donor chain of transplants or to a single recipient on the national transplant list, where the allocation criteria for deceased donor organs apply. (see figure 1). The UKLKSS was set up by NHS Blood and Transplant when the Human Tissue Act extended the scope of donor-recipient relationships beyond family and friends. Within the kidney sharing schemes, recipients who are incompatible by blood group or Human Leucocyte Antigen (HLA) type, with their living donor they can avoid antibody depleting treatments and improve transplant outcome if matched in compatible two-way (paired) or three–way (pooled) combinations of transplants with other donor-recipient pairs in a national pool. (see figure 2). Compatible donor-recipient pairs can also be registered in the paired/pooled scheme to achieve a better age or HLA matched transplant. The scheme allows living donor kidneys to be shared systematically and fairly across all four UK countries according to an algorithm that was developed in collaboration with colleagues at the University of Glasgow *(Dr David Manlove & Dr Gregg O'Malley)*. Through a continuous improvement programme, NHSBT has refined and adapted the algorithm and coordination of the UKLKSS to maximise the number of proceeding transplants identified in optimal combinations 200-260

donor-recipient pairs are included in every quarterly matching run and 30-70 compatible transplants are identified each time. When NDADs are entered into these matching runs, they can unlock up to three transplants in an altruistic donor chain. The NDAD donates to a recipient in the paired/pooled scheme, their paired donor donates to another recipient and so on, until the chain ends with a recipient on the national transplant list. Altruistic donor chains were first introduced in 2012, incorporating one paired couple (short chain) and extended into long chains, by adding an additional paired couple, in 2015. Between April 2007 to March 2016, 399 NDADs enabled 571 patients to be transplanted by donating either directly to recipients on the national transplant list or into altruistic donor chains.[1,2]

Figure 1: Options for Donating a Kidney as a Non-Directed Altruistic Kidney Donor

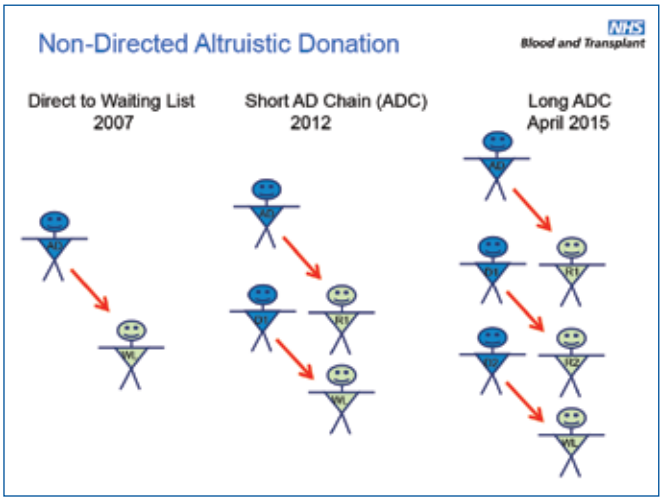
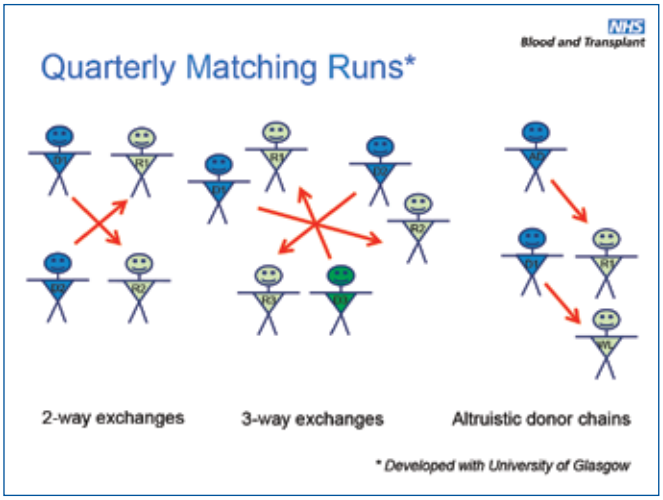


Figure 2: Options for Matching Compatible Pairs in Quarterly Matching Runs



With one of the most active NDAD programmes in Europe, there is a real opportunity to make a difference in terms of equity of access to LDKT and waiting times for patients with ESKD in need of a transplant.

Who Donates to a Stranger?

99% of NDADs are white; average age 50 years at time of donation[2]. Motivation varies but often stems from a general philosophy of life with commitment to organ, blood or bone marrow donation or it may be triggered by a personal experience that makes the person aware of the benefit of transplantation. The *'Give a Kidney'* charity, founded in 2011 to encourage and support non-directed donation, has a diverse membership but, in their view, they share a common bond: empathy and opportunity to donate. Previous research suggests that the outcomes for NDADs post donation are equivalent to those of family and friend donors[6]. NHSBT is currently collaborating in further research to explore the barriers and enablers to non-directed donation and the impact of anonymous donation on both donors and recipients.

Non-directed donation remains controversial but has become embedded in the UK LDKT programme, with participation from every transplant centre. In the past three years, NDAD rates have fallen from a peak of 117 to 83 per year. The decline in activity is being addressed through *'LDKT 2020'* but, despite the fall in donor numbers, it has been possible to maintain transplant activity as more NDADs choose to donate into the kidney sharing schemes.

Where next?

The implementation of *'LDKT 2020'*, aims to build on existing strengths to deliver a sustainable LDKT programme for the future. Non-directed donation has an important part to play and the aims are to:

- Increase awareness
- Ensure easy access to information and support for NDADs throughout the donor pathway from referral to life-long follow-up
- Encourage at least 75% of all NDADs to donate into an altruistic donor chain.

Non-directed donation has already been a catalyst for change within the UKLKSS and promises to remain so, allowing more patients to receive the transplant they need at the right time and with the highest chance of success.

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Further information:

NHS Blood and Transplant (NHSBT) – living organ donation: https://www.organdonation.nhs.uk/about-donation/living-donation

NHSBT latest statistics and annual activity reports: www.odt.nhs.uk

Give a Kidney charity: www.giveakidney.org.uk

Human Tissue Act and Human Tissue Authority: https://www.hta.gov.uk/our-role-living-donation

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Vascularised Composite Allograft Donation

Hand and Upper Limb Vascularised Composite Transplantation (HUL-VCA) began in the modern era with the first such case in Lyon, France, in 1998, followed promptly by another case in Louisville, Kentucky in early 1999. Since then sporadic reports of HUL-VCA have occurred from units around the world and most of those in advanced nations have achieved long term survival (although the very first case from Lyon was rejected psychologically). The first HUL-VCA donation and transplant in the UK occurred in December 2012 in Leeds Teaching Hospitals NHS Trust (LTHT).

Planning

The Leeds Surgical Team headed by Professor Simon Kay began working with NHSBT Organ Donation and Transplantation (ODT) in 2010 to look at progressing a Hand Transplant Programme. Many months of planning and meetings between ODT and LTHT followed to develop the transplant programme and those aspects of the donation process that would involve the Specialist Nurses – Organ Donation (SNOD). These included the protocols for hand assessment, blood sampling for Human Leukocyte Antigen (HLA) typing, the retrieval process and the media interest that would follow. In addition to this the National Organ Retrieval Teams (NORS) were informed and local NORS teams in the North of England consulted regarding the retrieval process. Simon Kay and his surgeon colleague Dan Wilks designed a retrieval protocol aimed at minimally interfering with solid organ retrieval, and indeed the whole thrust of those directing this new transplantation procedure was to achieve their goals with making only a positive impact on Solid Organ Transplant (SOT) donation and retrieval.

In addition to many meetings with SNOD teams, Professor Kay and Dan Wilks met with Clinical Leads in Organ Donation (CLODS), who are intensive care clinicians who together with the SNODs, lead on Organ Donation within the hospital trusts and via the trust's Organ Donation Committees (ODC). The CLODS, SNODs and ODC's were approached and informed of the very specific requirements of the programme, which necessarily included inspection of the upper limb before accepting the donation since appearance is a key factor in preventing psychological rejection after transplantation. In November 2011, LTHT issued a press release informing potential patients that they were progressing the hand transplant Service, and went 'live' in December 2012 at Leeds Teaching Hospitals.

Training

The SNODs are all specially trained in approaching potential donor families to gain consent for solid organ and tissue donation. At this time within ODT the SNODs were trained in the breaking bad news conversation and the approach to families by Verble, Worth and Verble[1]. Hand donation was new and to most within the Yorkshire Donation Team quite a daunting prospect of how, when and what to say to the donor family in the approach conversation. The team therefore had a bespoke training day with Verble, Worth and Verble exploring the language to be used when approaching a family for hand donation and at what point in the approach conversation hand donation should be mentioned. The SNODs were to use their judgment with potential donor families and if families were positive to the idea for tissue donation as well as solid organ donation they would be approached regarding hand donation.

Approach

Due to the specific needs and requirements of the patients on the hand transplant waiting list, not all potential organ donors are suitable to approach for hand donation. Only patients who are potential DBD (Donation after Brain Death) donors within specific agreed criteria are approached. These DBD patients still have a heart beat and therefore limb perfusion up until the point of retrieval, so reducing the duration of warm ischaemic time compared with donation after circulatory death (DCD). Alongside solid organ donation there are other absolute and organ specific contraindications which also reduce the number of potential donors who can be approached.

Following the first successful donation and transplant in December 2012[2], the programme was expanded to hospitals within the Yorkshire region within an hour of Leeds Teaching Hospitals. Despite further approaches and subsequent family consents for hand donation there remained only one hand donation and transplant due to either family decline for hand donation or the donor and potential recipient being an unsuitable match.

Expansion of the Hand Transplant Programme

In April 2016, Leeds Teaching Hospitals were awarded national funding from NHS England for hand transplantation[3]. Professor Kay will work in partnership with Oxford University Hospitals NHS Foundation Trust. The service in Oxford will undertake assessments and non-surgical elements of follow-up care to deliver a national service for hand transplantation. The requirement to deliver a national service necessitated that potential donors be sought from potential donors outside of the Yorkshire donation region. This expansion saw potential donor families approached in hospitals within the neighbouring organ donation regions of the Northern and North West donation teams. July 2016 saw the UK's first double hand transplant performed[4].

Although consent for hand donation is not a regular occurrence there continues to be an ongoing partnership between NHSBT and Professor Kay and Leeds Teaching Hospitals to ensure the hand transplant programme is successful and more patients receive this life changing transplant.

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4. www.bbc.co.uk/news/health-36858169

Case Study – Fiona Killick's Story

Fiona Killick needed a blood transfusion after her ultra-rare blood disorder left her at risk of death and 'looking like a smurf'.

Fiona was born with methaemoglobinaemia. Her blood contains higher levels of a form of haemoglobin that has a reduced ability to carry oxygen.

Fiona was told that when she was born, there were only two other people in the country with the congenital form of the condition and there are still very few known cases. Some people can acquire it through reactions to various substances which can be treated and cured.

Fiona had a blood transfusion as a baby, but through most of her life, Fiona did not need any treatment or experience any symptoms apart from sometimes looking a little blue (cyanosis).

However, as her pregnancy advanced in 2015 Fiona, an Assistant Headteacher at a primary school, began to suffer serious symptoms.

"Even when sitting down I was so out of breath I couldn't finish a sentence and had to take a breath between each word. Towards the end, my skin went bright blue and I looked like a smurf. Walking a few metres would leave me faint and so out of breath I would need to be put back on oxygen. As the days went past they also became increasingly worried about the baby as I was experiencing reduced foetal movements" recalled Fiona.

Fiona had multiple hospital visits to the John Radcliffe in Oxford and the Royal Berkshire Hospital in Reading, which included a spell in intensive care and she ended up spending most of the last two months of her pregnancy in hospital.

The doctors initially thought her problems were down to a bout of pneumonia she'd contracted, or related to some other lung infection or heart problem. By this time, at 28 weeks pregnant, her resting heart rate was 130 and the doctors were worried she would suffer organ and heart failure if her condition did not improve.

When Fiona did not respond to the intensive drug cocktails they were treating her with and began to deteriorate hour by hour, late on a Sunday night they decided to try a full red blood exchange, which was carried out by the Oxford based team from NHS Blood and Transplant's Therapeutic Apheresis Service. The blood was transfused through her neck, without painkillers so not to distress the baby, while she was in intensive care. The procedure took four and a half hours and 20 bags of A negative blood.

"Halfway through the exchange, my heart rate began to drop and my breathing became less laboured. By the end of the exchange my skin had started to turn pink again and I was able to talk in full sentences."

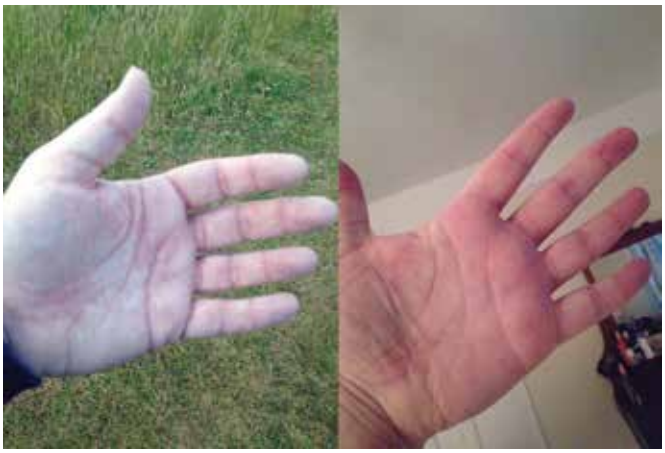
Fiona went on to have one more exchange before giving birth at 34 weeks, to her son Noah, weighing 4lbs 8oz, on July 30, 2016. Fiona said he is doing very well and is a healthy, smiley and very active baby.

Fiona said her doctors have been presenting her case at medical conferences as they are still unsure why her body reacted in this way. Congenital cases of the disorder are very rare and there are no recorded cases of issues during pregnancy. The hospitals did not actually have the equipment to record the level of the type of haemoglobin involved because the level was so high.

"If it hadn't have been for the red blood cell exchanges, the doctors don't think I or the baby would have survived," she said. "I don't think I realised how ill I was at the time, I was just trying to concentrate on breathing. Looking back now it was a very scary experience".

"If it wasn't for the very kind people who take the time to donate blood I wouldn't be here and my son wouldn't have his mother. Thank you from the bottom of my heart."

Fiona Killick



Fiona's hands before and after transfusion.

Voice of the Customer

Echoing the Voice of the Customer in NHS Blood and Transplant's Services

Bringing the voice of the Hospital Transfusion Laboratory into NHS Blood and Transplant (NHSBT) is a key role for NHSBT's Hospital Customer Service Managers. The voice includes customer satisfaction, compliments, feedback and complaints. A regular satisfaction survey provides one of the key strands of hospital customer feedback.

Every quarter, NHSBT Customer Services send an electronic Satisfaction Survey to capture feedback from hospitals. The survey represents the level of customer satisfaction using a score of 1-10 (1 = totally dissatisfied, 10 = totally satisfied). The proportion of customers scoring services at nine or 10/10 are reported throughout NHSBT and are referenced as top box scores.

The survey is issued to Transfusion Laboratory Managers in NHS and private hospitals served by NHSBT. Half of all hospitals are surveyed each quarter so that each hospital is surveyed just twice a year. The survey currently consists of 16 core questions that are repeated in each survey with a small number changing over time. Hospitals are also given the opportunity to provide free text comments including suggestions for improvement.

The questions broadly represent the customer journey with NHSBT, starting with the selection of components, through fulfilment, to delivery and support. These stages form the customer's whole experience and give a perspective on how easy, or not, we are to do business with.

	2016/17			Q3 16/17
% Top Box Scores	Q1	Q2	Q3	Ave Score
Components - Quality and Range	82	74	**90**	**9.3**
Ordering	83	84	**88**	**9.2**
Component Availability	58	53	**72**	**8.9**
Hospital Services	82	77	**90**	**9.2**
Delivery – Routine	56	46	**58**	**8.4**
Delivery - A Hoc	55	48	**68**	**8.6**
Delivery – Emergency	78	85	**89**	**9.2**
RCI - Referral process	60	67	**68**	**8.8**
RCI - Turnaround time	51	47	**61**	**8.5**
RCI – Report	55	57	**51**	**8.6**
RCI – Overall	68	53	**74**	**8.6**
H&I Overall	73	79	**87**	**9.2**
Customer Service Support	70	76	**79**	**9.1**
Clinical Support	63	70	**68**	**9**
Overall Satisfaction - NHSBT	75	67	**85**	**9**
Easy to do Business with	77	52	**71**	**8.9**

The latest survey was conducted with Hospital Transfusion Laboratory Managers in December 2016. The overall message is that we are performing well across most aspects of our services to hospitals and overall satisfaction is at an all time high point at 85% continuing a longer term improvement trend. 99% of customers report a level of satisfaction with the overall service.

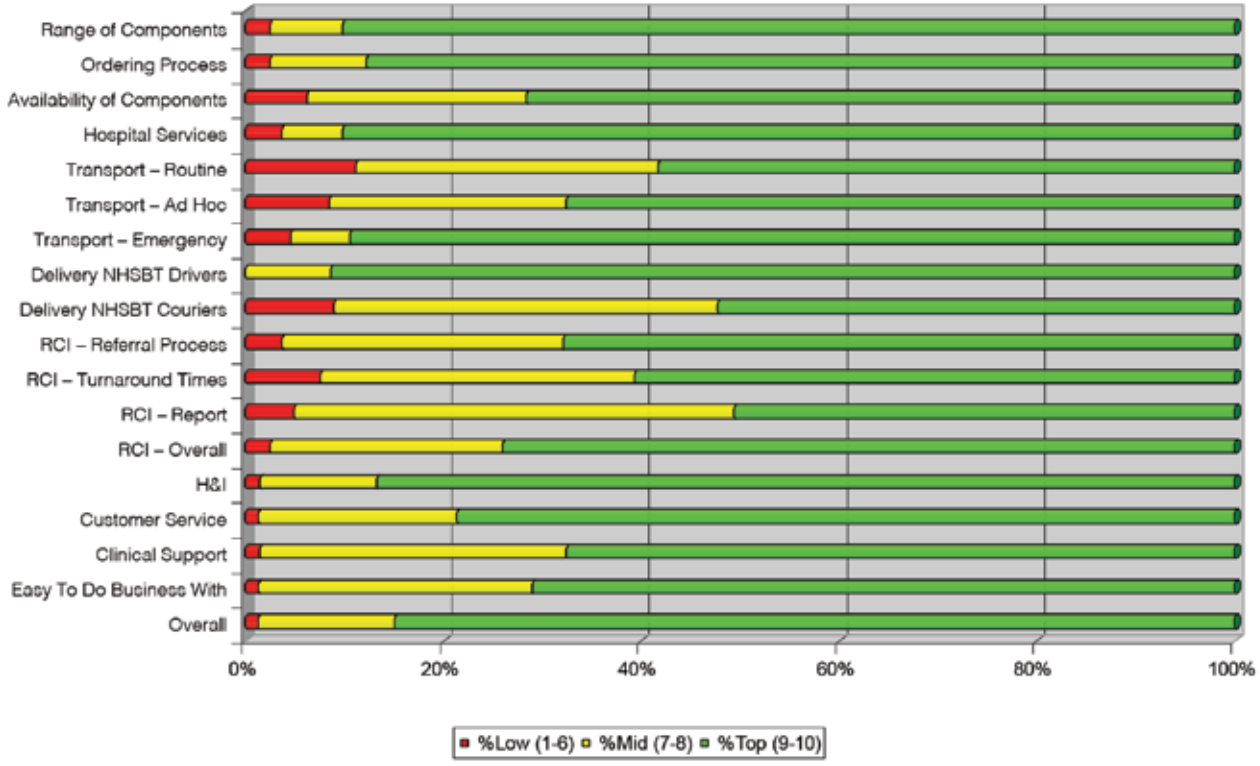
Diagnostic and Therapeutic Services – Satisfaction with Red Cell Immunohaematology (RCI) is very positive at 74%.The biggest improvement is seen with the turnaround time for testing and is a result of ongoing work by RCI to improve their performance. Although satisfaction with RCI reports appears to have dropped, the average score remains strong at 8.6 confirming a high level of satisfaction. This is due to a large number of respondents scoring eight rather than nine or 10, with few expressing any dissatisfaction. RCI deal with ~ 61000 samples per year. Histocompatibility & Immunogenetics and the provision of matched platelets continue to be well regarded with 87% of our customers rating us at nine or 10/10.

Manufacturing and Hospital Services – The results demonstrate a well-regarded service with high scores across each of the four indicators that cover range of components, availability, ordering and the interaction with Hospital Services. Component availability shows improvement whilst some challenges remain including the supply of A D negative platelets, some specialist components, a balance of K +/- and the supply of Hepatitis E Virus (HEV) negative units. 72% for component availability with an average score of 8.9 is an important general rating and reflects that NHSBT currently supply 96.5% of hospital orders on time and in full.

Transport and Logistics – A high level of satisfaction was achieved for our emergency delivery service with 89% of customers scoring nine or 10/10. The rating for routine deliveries, although variable, is trending upward and we are working with customers to review routine schedules and to rationalise ad hoc/collect patterns. Both routine and ad hoc deliveries remain a challenge especially when couriers are used. NHSBT drivers are highly regarded with a top box score of 91% and satisfaction with couriers has improved, scoring 52% compared to 34% for the last quarter. NHSBT handled 137,000 deliveries and supported 61,000 collected orders across 2016.

Customer Service and Clinical Support – NHSBT provide service and clinical support to hospital customers to ensure that components and services provided fit with hospital needs to support patient care. Every hospital has a Customer Service Manager link and 24/7 access to clinical support. Both services are well regarded as demonstrated by a continued upward trend in satisfaction.

Satisfaction in Context – This chart highlights, in green and yellow, the high levels of expressed satisfaction against low levels of dissatisfaction (red).



If we made one change

The survey goes on to pose a question to our customers; 'If we make ONE change to improve the service you receive, what should that be?'. Customer responses were collected around common themes that are broadly repeated from earlier surveys and other feedback. These themes suggest areas of action to enhance already well regarded services. For example, NHSBT need to do more to reflect a changing need for deliveries. Whilst fulfilment of orders is very high, more needs to be done to ensure the availability of some specialist components. The extended working day introduced by the RCI service has proven successful and provides opportunity for further improvement. NHSBT services are seen as being easy to interact with and staff are seen as friendly and helpful.

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CPD Questions

1. Blood and Fire:

Major Burns are:

a) Not associated with blood loss.

b) Only associated with blood loss at surgical debridement.

c) Only associated with late blood loss.

d) Associated with blood loss impaired erythropoietin response.

2. Immediate Blood Loss in the Absence of Surgical or Traumatic Bleeding:

a) Does not occur.

b) Blood loss in full-thickness burns of more than 10% of total body surface area, can be calculated at 10 plus 2% for every 10% full-thickness loss above 40%.

c) Acellular fluid losses outstrip red cell losses.

d) Blood loss outstrips Acellular fluid loss.

3. In Early Blood Loss:

a) Tranexamic acid has a role.

b) Viscoelastic clotting assays are commonly used.

c) Excision of large burns results in minimal blood loss.

d) Cell salvage techniques are often employed.

4. In Late Blood Loss:

a) Thromboprophylaxis is contraindicated.

b) Thromboprophylaxis is vital.

c) Only related to surgical bleeding.

d) Thrombocytopenia is a major factor.

5. Urgent Therapeutic Apheresis Procedures:

NHSBT:

a) Only provides Red Cell Exchange Therapeutic Procedure.

b) Only provides Leucodepletion Therapeutic Procedure.

c) Only provides Plasma Exchange Therapeutic Procedure.

d) Provides a range of Therapeutic Apheresis Procedures.

6. Urgent Therapeutic Apheresis Procedures:

a) There are no guidelines as to indication for Therapeutic Apheresis.

b) NHSBT use American Society for Apheresis Guidelines (ASFA) to establish indication for Therapeutic Apheresis.

c) According to ASFA Guidelines condition in category IV must have Therapeutic Apheresis immediately.

d) According to ASFA Guidelines condition in category I, Therapeutic Apheresis is harmful.

7. During the Audit Period:

a) Most more than 50% of cases receiving out of hours Therapeutic Apheresis usage met the audit standard.

b) All out of hours cases were due to sickle cell crisis.

c) Most out of hours cases were due to symptomatic hyperleukocytosis.

d) Most out of hours cases were due to hyperviscosity.

8. The Audit:

a) Recorded reasons for not accepting cases for out of hour's treatment.

b) Resulted in updating Therapeutic Apheresis Service on call Manual to include some additional diagnostic categories.

c) Resulted in anti-GBM Vasculitis dialysis dependent but without DAH to be included in cases heated overnight.

d) Resulted in HUS to be included in cases treated overnight.

9. Explaining Death Determined Using Neurological Criteria to Families:

a) There is no research evidence to support the belief that explaining 'brain death' well to families is positively associated with consent for deceased organ donation.

b) All families understand the term Brain Dead.

c) There is little in the way of research evidence on the exact words to use for a positive consent for deceased organ donation.

d) There is much in the way of research evidence on the exact words to us for positive consent for deceased organ donation.

10. The ATTOM Study:

a) So called because it is a small scale study.

b) Involves only one hospital.

c) Is the first and largest study of its kind.

d) Launched in 2017.

11. The Research Plan:

a) Has fine main work streams.

b) Only assesses survival on dialysis and after transplantation.

c) Will only look at patient reported outcome reassess of quality of life.

d) Will only assess access to transplantation.

12. The PITHIA Trial:

For renal transplant patients in whom kidneys to work at all, there is an average 1-year mortality of:

a) 5%.

b) 10%.

c) 15%.

d) 25%.

13. Majority of potential UK deceased kidney donors are now:

a) Under 40 years old.

b) Over 60 years old.

c) Under 50 years old.

d) Under 20 years old.

14. PITHIA Trial:

a) Will assess the use of kidneys donated from older (ancient) Greek and Romans.

b) Will assess the post-transplant status by biopsy.

c) Aims to test whether having access to pre-implantation kidney biopsies will increase number of deceased-donor kidneys for transplantation.

d) Will use biopsy data already held in transplant registries.

15. The Contribution of Non-Directed Donations in Living Donor Kidney Transplant:

In UK

a) 44%.

b) 34%.

c) 26%.

d) 14%. Are living donors.

Clinical Case Studies

Case 1

- A 51 year old lady with Sickle Cell Disease attended the Red Cell Clinic, Hospital A in November 2005. She had a history of multiple painful crises.
- Transfusion history: Three exchange transfusions, one before childbirth.
- She is O Rh D Positive; antibody screen: Anti-E. Extended phenotype: R1r , S-, Fy (a-b-), Jkb-
- In October 2014, she was admitted to Hospital B with a Hb of 56 g/L. Blood Group: O Rh D Positive with an anti-E. Two units O Rh D positive, E- red cells transfused.
- Two months later, she was admitted again with a Hb of 54 g/L. Blood Group again found to be O Rh D Positive; Antibody panel.
- In January 2015 she was:
- Admitted with Hb 54 g/L.
- Blood Group – O Rh D Positive.
- Anti E and which additional Antibody.
- Anti-D.

Questions:

1. What Test(s) would you do next?
2. What is the RhD type as:
   A. Patient?
   B. Donor?
3. What Measures should the laboratory take?

- **In January 2015**
- Admitted with Hb-54 g/l
- Blood Group – ORhD Positive
- Anti E and which additional antibody

ID panel profile

	Rh	M	N	S	s	P1	Lu^a	K	k	Kp^a	Le^a	Le^b	Fy^a	Fy^b	Jk^a	Jk^b	Patient
1	$R_1^wR_1$	0	+	0	+	4	0	+	+	0	0	+	0	+	0	+	2+
2	$R_1^wR_1$	+	+	+	0	0	0	0	+	0	+	0	+	0	+	0	3+
3	R_2R_2	0	+	0	+	2	0	0	+	0	0	+	+	0	0	+	3+
4	r'r	+	0	+	0	0	0	0	+	0	0	+	+	0	+	0	–
5	r''r	+	0	+	0	2	0	0	+	0	+	0	0	+	+	0	1+
6	rr	+	+	0	+	2	0	+	0	0	+	0	+	0	+	0	–
7	rr	+	0	+	0	0	+	+	+	0	0	+	0	+	+	0	–
8	rr	+	0	0	+	0	0	0	+	+	0	+	0	+	0	+	–
9	rr	0	+	+	0	2	0	0	+	0	+	0	+	0	0	+	–
10	rr	0	+	0	+	4	0	0	+	0	0	+	0	+	0	+	–
	AC																

Case 2

- 24 year old female.
- Diagnosis of Wilson's Diease, deceased donor Liver Tranplantation on 15/08/16.
- Patient's blood group B Rh D Positive.
- Donor's blood group B Rh D Negative.
- Around day ten, post transplant: Possible acute rejection; Methyl Prednisolone Pulse Therapy initiated. Patient on Tacrolimus.
- Test results confirmed haemolysis – Haemoglobin 124 (21/8 decreasing to 70 (27/8; LDH 4+ (IgH).

Questions:

1. What test would you recommend and what do you think it will reveal?
2. What group red cells would you recommend?

Case 3

- Seven year old boy. Thirteen months after his second multivisceral organ transplant (liver, small and large bowel and pancreas and stomach develops severe anaemia.
- Haemoglobin 24 g/L, platelet 1026, WBC 52 (neut 34).
- Reticulocytes 147 (20%), Bilirubin 74.
- Film: Spherocytes; nucleated RBC +++.
- LDH 2067 iu/l, Haptoglobin less than 0.1 g/L.
- DAT: See table.

Serology

Test	Result
Bio-Rad gel IAT/Enzyme	+++ / +++
Tube DAT, saline, 37°C	IgG 0; C3d +++
Direct agglutination, saline, 4O°C	0
Agglutination at 30°C	1 of 6 cells positive, no specificity
LISS tube IAT at 37°C: – With neat plasma – With DTT-treated plasma	 +++ +
LISS tube IAT (37O°C), after three alloadsorption rounds	No alloantibodies
Indirect Donath-Landsteiner test	0

Question:

1. What could be the cause of AIHA in this case?

Answers to Clinical Cases

Case 1

1. Perform ALBAclone panel ID profile.

	Weak D	DII& DNU	DIII	D IV	D V	DCS	D VI	D VII	DOL	DFR	DMH	DAR	DAR-E	DHK DAU4	DBT	Ro	Patient
A	+	+	+	+	+/–	+	–	+	+	+	+	+	–	–	–	+/–	+/–
B	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+
C	+/–	+	+	–	–	+	–	+	–	–	+	–	–	–	–	–	–
D	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+
E	+	+	+	–	–	+	–	+	+	+	+	–	–	–	–	–	–
F	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+
G	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+
H	+	–	+	–	+	+	+	+	+	+	+	+	+	+/–	–	–	+
I	+/–	+	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–
J	+	+	+	+	+	+	–	–	–	–	(+)	–	(+)	+	+	–	+
K	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	–	+
L	+	+	+	+	+	–	–	+	+	–	+	+	+	–	+	–	+

2. A. Negative as Patient.

   B. Positive as Donor.

3. A. Blood group changed to O RhD Negative.

   B. Two units O Rh rr, Kell negative, HbS negative RCC issued.

C. Patient was issued the Antibody Card.

- She visited Nigeria from 05/03/15 to 06/05/15.
- On 05/04/15?: unwell, febrile.
- Diagnosed Malaria and treated with Artemether 80 mg+ Lumefantrin 480 mg and Proguanil 100 mg.
- On 10/04/15?: Severe anaemia (Hct 0.08); transfused with two units O Rh D positive blood.
- **She did not have a medical alert card at that time.**
- Urine became "orange coloured" and she was jaundiced.
- Haematocrit dropped to 0.05.
- On 27/04/15 and 28/04/15 she had a further four units, of O Rh D negtive red cells.
- **This time she had the medical alert card on her.**
- On 07/05/15 she attended Haematology Out Patients with acute renal failure. Admitted to hospital.
- Anti D+E identified in plasma.
- DAT positive (3+) with IgG specificity.
- Anti D + E detected in the eluate.

Learning Points:

- Variant *RH* genes are common in patients with Sickle Cell Disease and may be missed by routine blood grouping.
- Patients with many D variants are capable of producing allo-antibodies to missing epitopes, if transfused with D positive red cells.
- Anti D made by persons with RhD variants have been responsible for Haemolytic Transfusion Reactions (as in the presented case) and severe Haemolytic Disease of Fetus and Newborn .
- **Patients, carry the antibody card with you!**

Case 2

1. A. Eluate: anti D.

   B. Antibody screen: anti-D.

2. A. Transfusion of B Rh D Negative red cells was recommended.

   B. The patient did not need further transfusions.

Learning Points:

- Non-ABO passenger lymphocyte syndrome: well recognised, although much rarer than PLS caused by ABO antibodies.
- PLS can be due to Rh (Mostly anti-D, but also – c, and –e), as well as Kidd, Duffy and, rarely, other allo-antibodies.

Case 3

- A warm-reacting IgM antibody?
- Serology of warm-IgM AIHA (Arndt PA et al, Transfusion **49**: 235-242, 2009)
- 37C agglutinin usually present.
- RBC coated with C3d
- RBC-bound IgM detected by tube in 14/47 cases by tube DAT, additional 15/21 by flow cytometry.

Complement deposition in auto-immune hemolytic anemia is a footprint for difficult-to-detect IgM autoantibodies.

Elisabeth M. Meulenbroek, Masja de Haas, Conny Brouwer, Claudia Folman, Sacha S. Zeerleder, Diana Wouters.

Haematologica November 2015 **100**: 1407-1414; doi:10.3324/haematol.2015.128991

- Detection of IgM auto-antibodies can be challenging. We set out to improve the detection of anti-erythrocyte IgM.
- Direct detection using a flow cytometry-based approach did not yield satisfactory improvements.
- Next, we analyzed whether the presence of complement C3 on a patient's erythrocytes could be used for indirect detection of anti-erythrocyte IgM. To this end, we fractionated patients' sera by size exclusion chromatography and tested which fractions yielded complement deposition on erythrocytes.
- We found that all patients with C3 on their erythrocytes according to standard diagnostic tests had an IgM anti-erythrocyte component that could activate complement, even if no such auto-antibody had been detected with any other test.
- This also included all tested patients with only IgG and C3 on their erythrocytes, who would previously have been classified as having an IgG-only mediated autoimmune hemolytic anemia.
- In conclusion, complement activation in autoimmune hemolytic anemia is mostly IgM-mediated and the presence of covalent C3 on patients' erythrocytes can be taken as a footprint of the presence of anti-erythrocyte IgM.

CPD Blood and Transplant Matters

Answers Issue 50

1. D	2. B	3. C	4. A	5. B
6. C	7. D	8. B	9. D	10. A
11. C	12. B	13. D	14. D	15. C

AMENDMENT FROM ISSUE 50:
With reference to 'Demand for O D Negative Red Cells How the Patient Blood Management Teams are Supporting the Challenge'

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Dr Robert Webster
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Editor
Blood and Transplant Matters
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23rd February 2017

Dear Dr Webster

The article printed in the January edition of Blood and Transplant Matters "Demand for O D Negative Red Cells – How the Patient Blood Management Teams are Supporting the Challenge" outlined the efforts of NHS Blood and Transplant (NHSBT) to support hospitals in the management of O D negative red cells and improve appropriate supply. However the data provided in the section 'Substitutions' did not provide an accurate picture of progress in this area by NHSBT.

The demand for the Rh phenotype Ro has increased from the 2,000 units per month stated in the article and has almost doubled to a demand of 3854 units in January 2017. This large increase in demand has provided a particular challenge but NHSBT has been making improvements to address this issue and the number of Ro units collected has risen from 2400 to approximately 2800 per month. In addition, the level of 'On Time in Full' (OTIF) issues have been over 50% since November 2015 rising to 52% in January 2017 (the article had stated 45%).

With regard to substitutions, previously when NHSBT was unable to meet a Ro request, O rr units were used as an alternative. However for the past year we have been working with clinical colleagues to develop a Ro substitution matrix. The matrix provides a clear guide to select the most appropriate substitutions for different Ro groups and includes using Ro of a different group prior to the use of rr donations. This has resulted in better use of both Ro and rr units. For example Arr donations are now used in preference to Orr donations for an A Ro request. This substitution matrix was shared with all hospitals in the June 2016 issue of The Update. For further information please see. http://hospital.blood.co.uk/media/28342/the-update-june-2016.pdf

Thank you for the opportunity to clarify key messages. It is apparent from this information and the information submitted in the previous edition, that NHSBT teams and hospitals are collaborating and working hard to support the challenges associated with the supply and the appropriate use of O D negative red cells.

Yours sincerely

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Business Disability Forum
Building disability-smart organisations

POSITIVE ABOUT DISABLED PEOPLE

Diary Dates 2017

6 June
1st Pan.London Haematology – Oncology Guidelines and Education Meeting
Location: UCH Education Centre, London
For more information contact:
www.b-s-h.org.uk

7 June
Clinical Laboratory Haemostasis 2017 UK NEQAS for Blood Coagulation Annual Scientific participants Meeting
Location: Sheffield Hallam University, The Atrium Conference Centre, Sheffield
For more information contact:
www.ukneqas.org.uk

8–9 June
Scot Blood Annual Conference
Location: The University of Stirling, Stirling
For more information contact:
www.scotblood.co.uk

9 June
12th Cambridge Summer Haematology Meeting
Location: Moller Centre, Cambridge
For more information contact:
www.b-s-h.org.uk

14 June
World Blood Donor Day
For more information contact:
www.who.int/worldblooddonorday

22 June
London Rare Blood Day
Location: Marriot Hotel, Regents Park, London
For more information contact:
www.b-s-h.org.uk

12 July
Annual SHOT Symposium
Location: Rothamsted Centre for Research and Enterprise, Harpenden, Hertfordshire
For more information contact:
www.shotuk.org

24–27 August
ISEH Society for Hematology and Stem Cells 46th Annual Meeting
Location: Frankfurt, Germany

8–9 September
ASH Meeting on Hematologic Malignancies
Location: Chicago, Fairmont Chicago, Millennium Park
For more information contact:
www.hematology.org

13–15 September
BBTS Annual Conference
Location: Scottish Event Campus, Glasgow, Scotland
For more information contact:
www.bbts.org.uk

16 September
World Marrow Donor Day
For more information contact:
www.worldmarrowdonorday.org

7–10 October
AABB Annual Meeting
Location: San Diego, California
For more information contact:
www.aabb.org/annual-meeting

Notes

CPD Blood and Transplant Matters Answers Issue 51

1. D	2. C	3. A	4. B	5. D
6. B	7. A	8. B	9. C	10. C
11. A	12. D	13. B	14. C	15. A

Notes

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