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6

Do Blood Group Antigens Play A Biological Role?

Garratty G
American Red Cross Blood Services, and University of California, Los Angeles, CA

There have been thousands of publications purporting to show an association of blood group antigens (BGAs) and disease. Most of these are statistical associations of ABO with various conditions. The first report was as early as 1917. Many of these studies were small and/or not repeatable, but some were large studies and/or the results have been duplicated by many investigators. Although some of the associations seem more akin to astrology than science, others appear now to have a scientific rationale. Some areas of interest have been: BGA associations with 1) malignancy (e.g., BGAs as tumor antigens and adhesion molecules enhancing metastatic potential; 2) receptors for parasites (e.g., malaria/Duffy), bacteria (e.g., *E. coli*/P, *H. pylori*/ABH, Le); viruses (e.g., Parvovirus B19/P, HIV/ABO, Le); 3) coagulation (e.g., bleeding/O↑, thrombosis/A↑, Factor VIII/A↑, vW factor/A↑; immunological ligands (e.g., complement/Bg, Ch, Kn, McC, Yk, Cr; adhesion molecules/s-Le^x, Lu, In^b (CD44); cytokines/Duffy; integrins/LW). Most of these associations relate to cells other than RBCs, but BGAs may perhaps sometimes play a role as functional molecules in the RBC membrane. Rare null phenotypes sometimes have abnormally shaped RBCs (e.g., Rh_{null}/stomatocytes; McLeod syndrome (Kell)/acanthocytes; Leach phenotype (Gerbich)/elliptocytes). RBC BGAs act as receptors for microbes, cytokines and complement. Others are associated with enzyme activity (e.g., Yt, Kell) and membrane transport proteins (e.g., anion transporter/Di,Wr; water transporter/Co; ammonia transporter/Rh; urea transporter/Jk). Some BGAs (LW, Lu, In^b, Ok^a, Xg^a) may be important cell adhesion molecules in erythropoiesis. Finally, some acquired BGAs are associated with disease (acquired B/colon cancer; T, Tk, Th, VA/infection, NEC, HUS; Tn/thrombocytopenia, hemolytic anemia; Th/congenital hypoplastic anemia). Although few of these associations prove that BGAs have a function, a picture is emerging that strongly suggests that many BGAs may play a biological role.

20

Bacterial Contamination

Murphy WG
Irish Blood Transfusion Service, Dublin

It is now becoming generally accepted that effective action is required to address the problem of bacterial contamination in platelet units, which causes death in up to 1 per 60,000 transfusions. There are three levels of action possible with varying efficacy and costs. Firstly, optimisation of donor arm cleansing and diversion of the first 30 units of the collection have the potential to reduce sentinel events such as positive cultures in quality monitoring programmes several fold, at marginal costs. Secondly, testing for contamination early in the platelet storage period will detect a considerable proportion of contaminated units, particularly those containing rapidly proliferating organisms. The limitations of available detection programmes include the necessity to release products from the Blood Centre before the result of the test is available, and the limited sensitivity. Costs are moderate, from 20 to 40 NZD per unit. While several national or regional programmes offset these by extending the platelet storage period to 7 days, the safety of this approach has not been satisfactorily demonstrated. Lastly, several proprietary

systems are in development that appear to have close to 100 per cent effectiveness in eradicating bacterial contamination from platelet units. At a cost of several hundred NZD per therapeutic dose, at least 10 percent of platelet recovery, and some concern over long term toxicity these systems are likely to gain widespread acceptance eventually and Blood Services need to begin planning their strategies.

21

Blood Safety – opportunities and costs

Sher GD
Canadian Blood Services, Ottawa, Canada

Transfusion medicine has undergone many changes in the past two decades, largely in response to the threats of HIV and HCV transmission. Owing to changes in donor risk factor screening, expanded donation testing and increased regulatory oversight, the risk of transfusion transmitted viral infection has decreased dramatically. While viral risks have attracted most attention, clinically significant noninfectious risks remain a concern, with fewer interventions aimed at their reduction. This presentation explores several paradigms of blood safety and interventions aimed at risk reduction. Early interventions aimed at reducing risks of transfusion transmitted viral infections yielded substantial numbers of positive donors, using relatively inexpensive technologies, and are thus deemed by all measures to be cost-effective interventions. As additional measures (e.g. NAT testing) are applied to the same risks, the paradigm of *diminishing returns* or increasing marginal cost takes effect, as cost-effectiveness of these interventions becomes increasingly poor. Some risks to blood safety are theoretical, or are at best unquantifiable, and in certain situations (such as variant CJD risk), donation testing is not available to reduce this risk. It is here that the transfusion world has adopted the paradigm of the *precautionary principle*. While the legacy of recent lapses in blood safety may be behind this precautionary approach, it is too early to say whether these measures will afford any benefit to transfusion recipients. In still other circumstances, interventions have been developed and approved that are of obvious benefit to some recipients, such as prestorage leukoreduction of cellular components for immune compromised persons. It is the issue of *restricted versus universal application* of such an intervention that frames the question around this paradigm. Other emerging threats to blood safety pose yet other paradigm challenges. In the case of West Nile Virus, seasonality of infection raises the question of *restricted (time / geography) as opposed to global testing*. Sensitized by previous failures to protect public safety or satisfy public concern, those charged with setting and implementing public policy are increasingly being accused of leaping into action in the absence of sound evidence, and at great cost to society. This may at times be appropriate. However since resources in all societies are finite, rational public policy aimed at improving blood safety must be based on considered, but swift analyses of actual advantages and disadvantages to the population that consider the level of resources available, and the implications of inappropriate allocation of those resources.

31

Tissue Factor: receptor function in sepsis and inflammation

Tipping PG, Sharma L
Monash University Department of Medicine, Monash Medical Centre, Clayton, Victoria, Australia

Tissue factor (TF) is a trans-membrane protein with structural similarities to class II cytokine receptors. The extra-cellular domain of TF binds factor VIIa and this complex is the principal initiator of coagulation in vivo. The binding of TF with factor VIIa also has important functions independent of coagulation. These include roles in embryogenesis, tumor angiogenesis and metastasis, cell adhesion and inflammation. The possibility that signaling via the short intra-cytoplasmic domain of TF contributes to these functions has been largely discounted. Indeed, the recent production of viable phenotypically normal mice lacking the cytoplasmic domain of TF ($TF^{\delta CT/\delta CT}$ mice) demonstrates that this portion of the molecule is not required for embryogenesis or normal growth and development (Melis et al, Biochem. Biophys Res Commun, 2001, 286: 580). These mice have normal levels of coagulation factors and normal coagulant function. However, studies of innate and adaptive immunity and endotoxaemia in mice lacking the cytoplasmic domain of TF indicate a role for the cytoplasmic domain of the receptor in modulating immune/inflammatory responses. Compared to wild type control ($TF^{+/+}$) mice, macrophages and neutrophils from $TF^{\delta CT/\delta CT}$ mice showed decreased production of reactive oxygen species following in vitro stimulation. Sensitised $TF^{\delta CT/\delta CT}$ mice showed reduced antigen-specific cutaneous delayed type hypersensitivity (DTH) responses to three different antigens (methylated BSA, ovalbumin and PPD) following subdermal challenge. Antigen-induced leukocyte rolling, adhesion and transmigration in postcapillary venules (assessed by intra-vital microscopy) was reduced in sensitised $TF^{\delta CT/\delta CT}$ mice and circulating antibody levels to all three antigens were also reduced. The in vivo relevance of these alterations in immune/inflammatory functions was assessed using a model of endotoxaemia. Mice were challenges with endotoxin (*E.coli* serotype 0111:B4, 0.5mg i.p). $TF^{\delta CT/\delta CT}$ mice showed greater survival at 24 hours compared to $TF^{+/+}$ mice. Serum levels of TNF-α and IL-1β were lower at 1 hr after endotoxin challenge and IL-6 levels were lower at 24 hours in $TF^{\delta CT/\delta CT}$ mice compared to $TF^{+/+}$mice. Neutrophil recruitment into the lung was also reduced in endotoxic $TF^{\delta CT/\delta CT}$ mice and endotoxin induced leukocyte rolling, adhesion and transmigration in post capillary venules was also reduced. Nuclear extracts from tissues of endotoxemic $TF^{\delta CT/\delta CT}$ mice also showed reduced NFκB activation. These results demonstrate that the cytoplasmic domain of TF contributes to both innate and adaptive immune responses and to recruitment and activation of leukocytes and death following endotoxin challenge in mice. They suggest that TF may augment immune/inflammatory responses via cytoplasmic domain dependent signaling.

41

Transfusion Support for Stem Cell Transplant (SCT) Patients

Pamphilon DH

Institute for Transfusion Sciences and Royal Hospital for Children, Bristol, UK

The number of SCT procedures performed each year continues to increase (19576 in 2001 compared to 12101 in 1995) according to data reported to the EBMT. SCT patients require extensive support with blood components (BC). The specifications and

transfusion thresholds for BC must be clearly defined. Prevention of CMV acquisition in SCT patients is essential and can largely be achieved by leucodepletion or CMV serology testing. Bacterial contamination of BC is more common than viruses in transmission of infection (TTI) before and after transplant and many centres have introduced measures including testing to reduce this. Novel pathogen and leucocyte inactivation strategies offer great promise in the prevention of TTI and transfusion-associated (TA) GVHD. The use of G-CSF after SCT to shorten the duration of neutropenia is accepted practice but the place of erythropoietin and thrombopoietic cytokines remains to be defined. One option to reduce thrombocytopenia post-SCT is the ex vivo generation of autologous or allogeneic megakaryocyte progenitors for infusion with or shortly after the graft. Selection of ABO compatible BC post-SCT where there is ABO incompatibility is critical - a simplified strategy can help to avoid excessive complexity and errors. Finally there is renewed interest in the use of prophylactic and therapeutic granulocyte transfusions in the setting of SCT. These issues will be discussed and up to the minute recommendations made.

42

Paediatric Transfusion

Savoia H
Women's & Children's Health, Division of Laboratory Services, Parkville, VIC, Australia

Many reviews of blood utilisation and transfusion practice for neonatal and paediatric patients have been performed. These reviews provide useful information regarding current practice and importantly highlight variations in practice. Very few studies provide sound evidence-based recommendations regarding when and how paediatric patients should be transfused. Clinical indications for fresh blood component transfusion in children and neonates will be discussed with emphasis on clinical situations which are unique to paediatric practice. A variety of red cell components exist with respect to anticoagulant and additive solutions. Platelets can be collected and prepared from whole blood or apheresis collections. Blood components can be modified through leukocyte reduction and irradiation and can be stored for varying periods. Selection of appropriate blood components for specific transfusion needs for paediatric and neonatal recipients can be confusing. Over years, common practices have developed which may or may not be appropriate or clinically relevant today. Selection of blood components for some specific clinical indications will be discussed.

51

Blood Safety – current issues in nucleic acid testing (NAT)

Heaton A
Chiron Blood Testing, Emeryville, California, USA

Introduction - The risks of the principal post- transfusion transmitted viral agents, HIV, HCV, and HBV, have been greatly reduced by EIA testing. However, residual risks remain because of the window period between viral exposure and 3rd generation EIA detectable antibody levels. To further reduce these risks, investigational (IND) blood donation testing for HIV-1 and HCV by NAT was introduced in the USA in 1999, using systems where donation plasma samples from whole blood were tested in mini-pools

(MPL) of 16 or 24. Based on NAT viral studies of sero-converting donors, the viral doubling time for HIV and HCV have been modeled at 21 and 15 hours; 3rd generation EIA window periods at 21 and 60 days; and the pre-MPL window periods at 11 and 10 days respectively. During the period April 1999 and April 2002, this approach has detected 10 HIV MPL+/EIA- donations (or 1 in 3.7 million donations) and 145 HCV MPL+/EIA- donations (or 1 in 260 thousand donations). More recently the potential for HBV NAT testing has been evaluated. WHO estimates that there are 350 million chronically infected HBV carriers worldwide, with prevalence rates varying from 1-2% in developed countries to >10% in high endemic areas. Donor incidence rates in repeat donors have been reported to range between 1.5 and 10/100,000 person years depending upon the country. The doubling time modeled from NAT tested sero-converting donors is 2.8 days, with an HBsAg EIA window period of ~59 days. Residual risk estimates based on the incidence of HBsAg+ seroconversion have a wide range (1 in 77,000 to 149,000 donations) because of application of adjustment factors to account for the variable duration of HBsAg antigenemia in acute resolving infection. Recently a new transfusion transmissible virus has been identified in the USA, the West Nile Virus (WNV). In June 2003, after a 9 month accelerated test development program, investigational WNV specific NAT assays were implemented throughout the USA. Method - To address the residual HBV risk, a triplexed NAT test, the Procleix ® Ultrio® assay that simultaneously detects HIV-1/HCV/HBV, was developed. The test system utilizes a Target Capture System with probes bound to magnetic particles that are specific for the three viruses. The amplification system utilizes a Transcription Mediated Amplification system similar to the Procleix® HIV-1/HCV assay. Detection involves a dual kinetic photoemission assay, which can simultaneously detect both internal control and positive sample signals. To assist procedural compliance, assay reagents include agents causing procedure based color changes, and the time to result is ~ 5 hours. Assay sensitivity studies were performed in 3 laboratories using WHO/Pelicheck standards diluted with virus free plasma. Reference sero-conversion panels were tested in two countries in pools of 1:8, 1:16, and 1:24, to compare with 3rd generation EIA detection. Results - 24 replicates were assayed at 8 different concentrations by 3 different technicians. WHO panel sensitivity [mean @ 95% probability, mean +/- range) based on probit analysis] is shown:

	Gen-Probe - USA	Lodi- Italy	EFS Tours - France
HIV-1 (IU/ml)	13.0 (10.1 – 19.5)	13.1 (10.5 – 18.4)	12.6
HCV (IU/ml)	1.6 (1.2 – 2.3)	2.3 (1.7 – 4.6)	2.7
HBV (IU/ml)	5.7 (4.8 – 7.0)	6.2 (4.9 – 8.8)	6.5

For sero-conversion panels, HBV DNA detection is reported as mean days earlier than

the Abbott PRISM chemiluminescence immuno (CIA) assay:

	Neat Sample	Pools 1:8	Pools 1:16	Pools 1:24
Gen-Probe USA	20 (11 – 43)	13 (4 – 29)	11.5 (0 –29)	Not done
Madrid Spain	28 (0 –94)	8.4 (0 – 22)	Not done	3.2 (0 – 11)

Discussion - HIV-1 and HCV sensitivities of the Ultrio® assay were comparable to the Procleix® HIV-1/HCV assay. Depending on testing pool sizes, HBV assay sensitivity was able to offer 10 – 24 day reductions in an estimated 45 –59 day CIA/EIA window period. Projected yields range from 1 –4 cases per 10^6 donations in developed countries.

53

ANZSBT Scientific Sub-Committee (SSC) Report 2003

Woodfield G, and Members of the SSC
Department of Molecular Medicine & Pathology, University of Auckland

This session is designed to enable the SSC to report back to ANZSBT members on progress made during the past year. In addition it presents an opportunity for members to ask questions of the sub-committee and to have input into the scientific direction of the SSC. The SSC has a membership of seven scientists and doctors. It meets regularly by teleconference and has occasional face-to-face meetings. For specific subjects requiring additional input, expert working parties are formed. In some projects there is co-operation with bodies such as the NH&MRC, and the Blood Services of Australia and New Zealand. All final reports are submitted to the Council of the ANZSBT before release. During the past year, projects have been completed on blood irradiation, laboratory tests for foeto-maternal haemorrhage, rhesus immuno-prophylaxis and a review of the pre-transfusion guidelines. Various publications on these matters have been produced. In progress are projects on paediatric and massive transfusion as well as guidelines for the use of granulocytes. Blood administration guidelines are being produced as well as charts intended for clinical guidance. Another subject of potential interest is transfusion in disaster situations. During this session, SSC members will present an update of specific activities as well as inviting comments from the audience.

59

Longitudinal Analysis of the Markers of Iron Status in Blood Donors

Heatley S, Doherty K
Australian Red Cross Blood Service, Adelaide, South Australia

Iron deficiency in blood donors is of major concern to Blood Services worldwide as it impacts on donor health, donor deferral rates and blood sufficiency. To manage iron deficiency the relationship between iron status and donation behaviour needs to be fully understood, while considering the age, gender and diet of the donor. Ferritin is the major storage protein of iron and is found mainly in the liver but is also present in normal serum. It is an indicator of the body's available storage iron and a serum ferritin concentration of <12ng/ml is considered diagnostic of iron deficiency. When iron stores have become depleted, higher levels of zinc protoporphryin are detected as the red cell substitutes zinc for iron and levels of soluble transferrin receptor (sTfR) are increased as iron becomes limited for the production of red cells. To clarify the relationship between iron status and donation behaviour 196 blood donors were recruited in January 2003. At each donation over the following twelve months a full blood count, serum ferritin, zinc protoporphyrin ratio (ZPR), sTFR levels and a short questionnaire regarding diet and vitamin supplementation was analysed. At the index donation, 23% of the donors were deferred due to ferritin levels <12ng/ml. As of May 2003, 43% had returned. Analysis

of the returned donors revealed a complex relationship between the number of donations and ferritin levels. The average reduction in ferritin was approximately 20% following a single additional donation. However some donors had an increase in ferritin levels, of these 20% were taking iron supplements at the first donation compared to 6% whose ferritin level was reduced. 19.6% of donors were deferred on the second donation. Of these donors, all had a serum ferritin level <25ng/ml on the first donation, with the majority (83%) having ferritin <20ng/ml. 54% of all donors had a serum ferritin level <25ng/ml. sTfR and ZPR analysis revealed a poor correlation with ferritin. Of the donors with ferritin less than 12ng/ml only 15% of the females and no males were identified by ZPR as being iron deficient. The positive predictive value of sTFR for detecting iron deficiency defined by ferritin levels <12ng/ml was 60% with a sensitivity of 60% and specificity of 72%. By assessing the relationship between different iron indices strategies may be developed to maximise donation potential whilst minimising risk of iron deficiency.

60

Effect of Storage on the Expression of Cell Surface Receptors on Young and Old Erythocytes

Healey G, Patton KA, Anniss AM, Sparrow RL

Research Unit, Australian Red Cross Blood Service, Melbourne

During storage of packed red blood cell (RBC) products, numerous morphological and biochemical changes occur to the erythrocytes. It is hypothesised that during storage older erythrocytes contribute more significantly to these changes. In this study we investigated complement regulatory molecules (C'RMs) and cell adhesion molecules (CAMs) which are cell surface receptors involved in the transmission of signals which may regulate the cell. The pattern of expression of these molecules changes during erythroid maturation leading to a low expression on mature erythrocytes. This study monitored the expression of these molecules on young and old erythrocytes over the 42-day storage period. Whole blood was collected from healthy donors (n=15) and processed into leucocyte-filtered RBC units according to standard procedures. The units were fractionated by centrifugation and the uppermost 50% of RBC (young) was decanted into one pack, the remainder (old) into another pack, then stored at 4^{o}C. Density of the samples was confirmed by their average specific gravity. In six RBC products after separation, autologous leucocytes were added to both fractions on day 1. Samples were collected on day 1, 7, 14, 28 and 42. Flow cytometry was performed at all time periods with PE or Fitc-conjugated antibodies to CD44, CD47, CD55, CD58, CD59 and CD147. All antibodies were titered to determine the optimum concentration prior to the study. The mean fluorescence of each antibody at each time period was obtained. Individuals had comparable levels of each CAM or C'RM expressed on the surface of their erythrocytes. The level of CAMs and C'RMs expressed was in general stable thoughout the 42 days of storage, although there were trends suggestive of a decrease with time. Old RBCs had a statistically significant lower expression of the C'RMs CD55 and CD59 compared to young RBC. The significance of these changes in expression of CAMs and C'RMs have on the survival of erythrocytes in stored RBC products is unclear. These changes may provide a positive signal for phagocytosis which could contribute to the clearance of transfused RBCs. Further studies of the role of CAMs and C'RMs on mature erythrocytes will aid in the understanding of their function and strategies to further improve the quality of RBC products.

61

Post-Partum Prophylactic Anti-D: can the recommended dose be reduced?

Fong EA, Augustson BM, Grey DE, Davies JI, Erber WN
Transfusion Unit, Western Australian Centre for Pathology and Medical Research, WA

National Health and Medical Research Council (NHMRC) guidelines currently recommend the administration of a standard dose of 600-625 IU of Rh(D) immunoglobulin to all Rh(D) negative mothers within 72 hours of delivery of a Rh(D) positive infant. This standard dose will protect against a bleed of up to 6mL of foetal cells into the maternal circulation. In a small study including 159 Rh(D) negative post-partum patients Raniol *et al* (HSANZ/ASBT/ASTH Conference 2002) proposed that a minidose of 250 IU Rh(D) immunoglobulin is sufficient in the majority of cases, covering a feto-maternal haemorrhage (FMH) of up to 2.5mL. We report a retrospective analysis of 4,075 maternal samples from Rh(D) negative mothers who had delivered a Rh(D) positive infant, tested between July 1999 and September 2003. Feto-maternal haemorrhage (FMH) was quantitated on each sample within 72 hours of delivery, using a Coulter Epics XL flow cytometer.

	Volume of FMH			
	< 1.0mL	1.0-2.49mL	2.5-5.99mL	> 6.0mL
No. cases (cumulative)	3,721	288 (4,009)	45 (4,054)	21 (4,075)
Mean volume	NA	1.5	3.7	14.4
% of cases (cumulative)	91.3 (91.3)	7.1 (98.4)	1.1 (99.5)	0.5 (100)

NA: not applicable

In 91.3% of cases the FMH was less than 1mL, and in 98.4 % the FMH quantitation was less than 2.5mL. A further 1.1% of post-partum cases were found to have a FMH of 2.5-5.99mL. This means that 98.4% of post-partum patients only need administration of a single 250 IU Rh(D) immunoglobulin minidose. This would have major benefits in terms of supply (calculated saving of 350IU x 4,009 = 1,403,150 IU for this cohort), and cost of anti-D prophylaxis. Current guidelines require that a standard dose of 600-625 IU Rh(D) immunoglobulin be administered post-partum which would cover a FMH of up to 6.0mL. Based on our data only 1.1% of post-partum cases have a FMH of between 2.5 and 5.99mL requiring the standard dose of 600-625 IU Rh(D) immunoglobulin. The introduction of flow cytometry as a routine method for FMH quantitation has provided accurate, reliable and reproducible results. Our data clearly shows that consideration should be given to changing the guidelines to incorporate the 250 IU Rh(D) immunoglobulin minidose as the recommended dose post-partum in conjunction with flow cytometric determination of FMH. The saving in Rh(D) immunoglobulin could be used for the production and supply of minidose 250 IU Rh(D) immunoglobulin for antenatal prophylaxis, a product currently in short supply and requiring importation from overseas commercial suppliers.

62

Prospective Community Study of Mannose Binding Lectin (MBL) Deficiency and Infection in Term Neonates

Dean MM[1], Williams BA[2], Heatley SL[1] and Minchinton RM[1]
[1]CRC for Vaccine Technology at the Australian Red Cross Blood Service Brisbane and Adelaide;
[2]Royal Childrens' Hospital Herston

Background: MBL is a circulating plasma protein that is a significant component of the innate immune system. It assumes particular importance when the adaptive immune response is compromised or underdeveloped. MBL is a multifunctional molecule that can act both directly as an opsonin, and in complex with its associated serine proteases (MASPs), it can activate the lectin pathway of complement to potentiate pathogen killing. Mutations in the *MBL2* gene and polymorphisms of the promoter region, lead to an MBL deficiency in approximately 25% of individuals. Aim:

- To measure MBL levels and complement activation capacity in term neonates at birth.
- To prospectively determine if MBL deficiency is a risk factor in infection in the first three months of life.

Methodology: Study population (n=191): Informed consent to participate in the study was obtained at prenatal classes. Cord blood was sampled at birth and analysed for MBL level, C4 deposition and MBL genotype. Infection in the neonates was followed over a three month period.

Control population (n=236):_MBL levels, C4 deposition and MBL genotype was determined in healthy adult blood donors. Results: At birth, neonates were found to have equivalent MBL levels and C4 deposition to adults. Neonates with viral and/or bacterial infection had significantly lower MBL levels (p=0.028) and C4 deposition (p=0.035) than neonates without viral and/or bacterial infection. Neonates with respiratory infection had significantly lower MBL levels (p=0.02) and C4 deposition (p=0.046) than those without respiratory infection. Neonates who suffered two or more infections during the first three months had significantly lower C4 deposition (p=0.015) than those with one or nil infections. A trend was observed towards lower MBL levels in neonates who had two or more infections, compared to those with one or nil infections, though this was not significant (p=0.052). MBL deficiency was not associated with severity of infection; there was no significant difference in MBL levels (p=0.32) or C4 deposition (p=0.23) in neonates requiring hospital admission or antibiotic treatment. Conclusions: In this prospective study, MBL deficiency in cord blood samples was associated with increased infection in neonates in the first three months of life. This was particularly evident for viral and/or bacterial infections and infections in the respiratory tract.

63

Drug Induced Haemolytic Anaemia Secondary to Repeated Administration of Oxaliplatin

Chen VMY, Thrift KM, Morel-Kopp MC, Ward CM, Flower RL
Northern Blood Research Centre and Pacific Laboratory Medicine Services (PaLMS), Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, Australia

Background: The platinum-based chemotherapy agents have been associated with an acute immune mediated haemolytic anaemia that is potentially fatal. The cause of positive direct antiglobulin tests and the mechanism of haemolysis with these agents remains controversial, and the specificity of this entity has not been previously defined. Case report: We report a patient who developed a DAT (direct antiglobulin test) positive intravascular haemolytic episode after a red cell transfusion was delivered during the infusion of her 17th cycle of oxaliplatin. Standard pretransfusion testing was uncomplicated, however post-infusion, the serum was no longer compatible with the transfused units, an IgG specific panagglutinin (4+) was present in the serum and an eluate from the red cells was panreactive. Results: Patient's serum taken 10 days after the reaction induced agglutination of all red cells tested using the indirect antiglobulin test, but only in presence of oxaliplatin (3+). The effect was retained with a purified IgG fraction and almost eliminated with IgG depleted serum. When patient IgG was incubated with oxaliplatin and free drug was depleted, agglutination was still observed. Agglutination was seen in the drug adsorption studies with high concentrations of oxaliplatin and patient serum. Immunoprecipitation analysis of biotinylated red cell membrane lysates revealed a band with the molecular weight of the Band 3 anion channel, only in the presence of patient serum and oxaliplatin. Conclusion: Our investigations indicate oxaliplatin interacts with an IgG antibody and a red cell membrane epitope, that the interaction of drug-antibody complex with antigen is likely to be Fab mediated and that a possible target is Band 3.

64

Country Inventory Management - introducing a quality framework to improve the storage and transport of blood

Jones D[1], Chapman P[2], Hetzel P[1]
[1]Australian Red Cross Blood Service -South Australia Adelaide, [2]Department of Human Services of South Australia, Adelaide

Aim: BloodSafe Country Inventory management is part of the BloodSafe project in South Australia. It has an overarching theme of 'Safety and Quality in Action'. Previous research has revealed inconsistencies in the storage and transport of blood in country hospitals resulting in its unnecessary wastage. The central aims of the Country Inventory management project are to:

a. improve the safety and quality of the blood supply to country hospitals
b. introduce a quality framework to support the redistribution of blood, thus reducing wastage through expiration of unused units.

Methods: A questionnaire was sent to all country hospitals. This was used to identify supply routes, storage facilities, types and numbers of products stored, and knowledge of storage and transport requirements. Qualitative data was obtained through a site visit to hospitals that held

stocks of blood. A collaborative group was formed consisting of key stakeholders involved in the supply of blood to the country hospitals, advisers from the Department of Human Services and Australian Red Cross Blood Service (ARCBS). Results: Based on findings identified from the questionnaire and site visits a quality framework has been developed. This consists of a series of procedures covering all aspects of the handling of blood from receipt, storing, packing, to return and documentation. There are also a series of registers for all products that will improve product traceability. This will facilitate any look-back queries. A logbook to record fridge maintenance has also been developed. These systems will act in support of the ARCBS Memorandum of Understanding (MOU) for the storage and transport of blood and will facilitate the re-distribution of blood between approved users, thus reducing wastage due to expiry. Conclusions: This project has revealed a variety of problems in the transport and storage of blood in country areas. It has provided a way forward, through the implementation of a quality framework, to improve standards. It will support the introduction of the MOU enabling the redistribution of blood and the concomitant reduction in loss of blood through expiry. The formation of a collaborative group of key stakeholders has improved liaison between hospital transfusion services, hospitals and the ARCBS.

72

From Dingoes to Dingbats: trials and tribulations in haematology

Carrell R
Department of Haematology, Addenbrooke's Hospital, Cambridge Institute for Medical Research, University of Cambridge, UK

Haematology is a branch of medicine that must necessarily move with the forefront of science. With this comes a requirement to make rational decisions in times of uncertainties and in a society that is in essence irrational. An early lesson came with the news in 1982, of the conviction of a young mother, Lindy Chamberlain, for the killing of her daughter. The conviction was substantially based on the identification of bloodstains, in a car left for 6 months in the sun in Mt Isa**,** as being of infant origin. It was obvious to experts in the haemoglobin field that this conclusion was beyond the limits of technology at that time. This was amply confirmed on review of the evidence, which fell far short of the standards required for acceptance in the most lax of scientific journals: with missing controls, lack of primary records and an inadequately supervised analyst who was unaware of her limitations. Yet a carefully written and documented account of these shortcomings was discounted by a judge, who readily admitted his scientific incompetence, and was dismissed by the prosecuting barrister as "seeking to kick field goals by moonlight – the game is over and the referee has gone home". As indeed he had! So lesson number 1 – do not necessarily expect justice on the basis of logic and truth. As will be described, justice was only achieved in the Chamberlain case by detective work outside the legal system that revealed step-by step the incompetence of the prosecution and its witnesses.
A second lesson from the 'dingo' case was the perils of trials carried out in an atmosphere of public indignation. A terrible example is the HIV/transfusion trials in Paris in 1991-3, amidst public hysteria, with the Clinical Director of the National Blood Transfusion Centre, in a televised incident, being forcibly tied to a tree and covered with red paint. The Director and the Head of R & D of the Centre were both imprisoned following trials that, as will be detailed, made a mockery of justice. Lives of good and caring doctors and scientists were destroyed while many of their colleagues just stood and watched. There are numerous risks ahead for our profession. The best safeguards are those that have so far defended haematologists in England and Australasia – a clear recognition of the science of haematology, coupled with a collegiality based on integrity and openness of communication.

74

Light from a Black Hole

Murphy WG
Irish Blood Transfusion Service, Dublin

A damning report published in 1995 followed by a Tribunal of Inquiry the following year clearly established that culpability in the Irish Blood Transfusion Service had caused the contamination of the national therapeutic Anti-D supply with Hepatitis C between 1977 and 1994. This had exposed tens of thousands of women to risk, infected over one thousand of them, and has caused several deaths. Monetary compensation has cost hundreds of millions of Euros to date. The BTS was exposed to an intense storm of public outrage over several years, manifest in the political and governmental processes, in the media, from the regulatory authorities, and from the public, individually and collectively. The effects within the blood service were traumatic. Blood supplies were very difficult to maintain; blood had to be imported from abroad on several occasions to meet needs, and all hospitals were asked to cancel planned surgery on several occasions; there were five different CEOs in five years, and almost all other top management jobs had a similar, if less intense, revolving door occupancy. Recruitment and retention of good staff was extremely difficult and morale was a vague memory. Nevertheless, throughout the second half of the 90s the commitment of many individuals at all levels to get the job done enabled the service to weather the storm and more or less recover. In the past two years supply has been restored, public confidence has improved and media attention waned; regulatory concerns have been, with one exception, resolved. Internally, however, the human resources problems have been almost overwhelming at times, and many remain unresolved, if not unresolvable. Morale, pride, and shared purpose are very slow in returning. However, the important lessons from a disaster such as this are not in how to survive them, but in how to avoid them. Ultimately years of under-resourcing, resulting in poor staffing numbers and training, bad management, no scientific or medical research activity and indifferent oversight and governance created stagnation and isolation and a disaster waiting to happen. In reversing the underlying entropy of an organisation such as a national BTS, resources, both fiscal and human, professional management and governance are necessary but may not be sufficient: an active programme to ensure international dialogue, awareness and participation is also essential.

75

Canada post-Krever: lessons learned

Sher GD
Canadian Blood Services, Ottawa, Canada

At the height of the largest public health crisis in Canadian history, in which thousands of Canadians were infected with HIV and Hepatitis C Virus, the Federal Government responded with an exhaustive inquiry into the events surrounding the “tainted blood scandal”. The *Commission of Inquiry on the Blood System in Canada*, headed up by Hon. Justice Krever, began in 1993 and produced its final report in late 1997. This seminal Royal Commission had, and continues to have, profound effects, and set upon the country a radical transformation of every aspect of the blood system. The regulatory framework, the operation of the blood collection / distribution system, and the practice of transfusion medicine all underwent fundamental changes in Canada, and the ramifications thereof continue to be felt internationally. The changes brought to the Regulatory environment have resulted in philosophical, policy, capacity and personnel

changes that today reflect in a Regulator operating under an increasingly solid risk management framework and with increasing responsiveness to industry, while at the same time ensuring compliance at a level hitherto not seen in Canada. The changes to the system, however, were most comprehensive in the sphere of the blood Operator. Two Operators now exist, Canadian Blood Services (CBS), accounting for about 75% of the system and operating in 9 Provinces and 3 Territories, and Hema-Quebec operating in the Province of Quebec. The underlying principles giving rise to the changes relate to: effective governance, clear accountabilities, independent decision making (arms length from funding governments), stable funding, contingency capacity for emerging threats, legitimate public participation and committed transparency. The service delivery model of CBS is undergoing major re-engineering, with *Transformation* of all core and support services, investment in technology, infrastructure and human capital. Stakeholders to the system, previously vehemently critical of it, are actively engaged at all opportunities, as is independent, international expertise. As a consequence of these changes, blood donation rates have increased 18% over 4 years, public trust in the blood system has increased significantly, media attention is almost exclusively positive, and the crisis is certainly over. The legacy, however, should never be forgotten, and the hard-earned trust is only as fragile as the capacity to respond to future emerging threats. This presentation will explain how the above principles have been translated into practice, will discuss the lessons learned post Krever, and how they guide the future direction of the blood system in Canada.

76

Transfusion Safety – can we afford the precautionary principle?

Merlyn S
Pall Corporation, Cheltenham, Australia

The Food and Drug Administration, and regulatory agencies elsewhere, are increasingly requiring the deferral of donors, both by test and by medical history, as a result of criteria based on the precautionary principle. At the center of this issue is how regulators should manage risk in the absence of certainty about the likelihood or magnitude of potential harm to transfusion recipients. A precautionary approach gained momentum, and international attention, with the publication of the Krever Commission Report in Canada. In the wake of that country's transfusion transmitted HIV epidemic, Justice Krever announced that "action to reduce risk should not await scientific certainty". Geographic exclusion of donors to reduce the risk of transfusion transmitted nvCJD is the most recent example of a precautionary regulation. This exclusion has resulted in a significant loss of donors and, since there are still no human cases of transfusion transmitted nvCJD, the regulation addresses a hypothetical risk. A precautionary approach has been proposed for other categories of donors, including those with factor V Leiden, those who have been exposed to xenotransplant recipients, and, with a view to reducing the risk of TRALI, those immunized to HLA antigens during multiple pregnancies. Given the current safety of the blood supply, indiscriminate application of the precautionary principle introduces new risks, in particular jeopardizing the adequacy of the volunteer donor base. While transfusion safety is an undeniably essential goal, it must not be achieved at the expense of the availability of blood and components.

84

Apheresis Symposium for Thrombotic Thrombocytopaenic Purpura: the pathophysiology of thrombotic thrombocytopaenic purpura and the implications for diagnosis and treatment

Pimanda JE
Centre for Vascular Research, University of New South Wales and the Department of Haematology, The Prince of Wales Hospital, Sydney

The recent discovery of the von Willebrand Factor (vWF) cleaving protease (ADAMTS13) and the association of its deficiency with thrombotic thrombocytopaenic purpura (TTP) has generated both enormous interest and considerable confusion. Ultra large von Willebrand Factor (UL vWF) multimers are present in the plasmas of patients with chronic relapsing TTP in remission but disappear during an attack. This observation led to the recognition that UL vWF multimers precipitate the thrombotic occlusion of arterioles, a feature that characterizes TTP. Initial management of patients with TTP is difficult because of lack of specific diagnostic criteria and high mortality without plasma exchange therapy and the risks associated with plasma exchange. Multiple mutations in ADAMTS13 are associated with congenital TTP and neutralizing autoantibodies have been demonstrated in the acquired TTP syndrome. Nevertheless, there is an enduring uncertainty about the specificity of ADAMTS13 deficiency for the diagnosis of TTP in adults and its value as a guide to treatment. Although a number of functional assays for this enzyme have been described, the more rigorously evaluated assays are difficult to perform outside a research laboratory. The cloning of the ADAMTS13 gene has also raised the prospect of recombinant enzyme therapy for the treatment of TTP, and this has heightened the need for a simple assay.

85

Adverse Reactions to Plasma and Plasma Products

Isbister JP
Royal North Shore Hospital, Sydney

Plasma components are rarely considered to be a major cause for adverse transfusion reactions. However, the complexity of plasma and its various components and alterations during component processing may be responsible for a broad spectrum of adverse effects. The antigenic heterogeneity of plasma proteins and the presence of alloantibodies makes plasma components potentially responsible for a wide range of immunological reactions, many of which remain poorly understood and commonly unrecognised or undiagnosed in clinical practice. Clinical severity may range from minor urticarial reactions or flushing through to fulminant cardiorespiratory collapse and death. Many of these reactions are probably true anaphylaxis, but in other cases mechanisms have been less clear and the confusing term anaphylactoid has been used. Adverse effects may be immunologically mediated due to donor plasma proteins containing epitopes on their proteins different from those on the recipient's functionally identical plasma proteins (eg anti-IgA antibodies). Alternatively antibodies in the donor plasma may react with recipient cellular or plasma components, the most serious being transfusion related lung injury (TRALI) due to donor leukoagglutinins. There may be physicochemical characteristics or contaminants of plasma products related to preservation, fractionation or storage, such

as temperature, chemical additives, medications and micro-organisms. The preparation techniques and storage conditions of blood and blood products may also cause adverse reactions through; the accumulation of metabolites or cellular release products (cytokines), plasma activation (eg complement and kinin/kininogen systems), histamine generation, chemical additives (ethylene oxide, formaldehyde, drugs, latex. As large volumes of plasma and/plasma substitutes are rapidly infused during plasma exchange procedures and awareness and early recognition of adverse events is important. Plasma exchange is a unique situation in which blood or blood products and plasma substitutes are being infused at resuscitation rates into conscious, normovolaemic and normotensive patients. The blood levels of many of the inhibitors and catabolic enzymes for the vasoactive substances mentioned above are reduced during plasma exchange and patients may be at increased risk for adverse reactions.

87

Issues of Psychological Control during Haematological Transplantation: early findings from a study in progress

Surgenor LJ[1,2], Horn J[1], Spearing R[2]
[1]Department of Psychological Medicine, Christchurch School of Medicine and Health Sciences, Department of Clinical Haematology, Christchurch Hospital, Christchurch

Control issues, and more generally, the ways people prefer to be in control of their lives are thought to be important in predicting psychological adjustment to cancer, patient compliance with treatment regimes, and subsequent quality of life. Although 'locus of control' measures have dominated this particular research, recent conceptual reviews point to the multifaceted nature of control, and accordingly, the importance of employing more sophisticated measures. Using one such measure, the purpose of this prospective study is to describe the control profile of a clinical population (n = 60-80) as they undergo and recover from a bone marrow or stem-cell transplantation. Specifically, the study investigates the relationship between psychological control (Shapiro Control Inventory), quality of life (EORTC QLQ-C30), and psychological distress (HADS) during transplant planning and then again one week after transplant, at hospital discharge, and 100 days after the transplant. While recruiting of participants continues for another year, early results after one year indicate that pre-transplant depressive symptoms are significantly associated with impaired beliefs in ability to attain control, a sense of loss of control, and impaired control in the domains of body, mind, self, and wider impulses. The point at which there is the greatest risk of clinically significant mood or anxiety symptoms is at hospital discharge. Issues such as 'locus of control', desire for control, or the methods by which people gain control, were not significantly associated with psychological distress. If these early trends are sustained, this would have implications for the form, content, and timing of psychological consultations with people undergoing haematological transplantation.

128

FAS Endoluminal Brushing a Novel Tool for Diagnosing Catheter Related Sepsis in Intravascular Tunnelled Indwelling Catheters

Sanders J
Clinical Haematology Department, Christchurch Hospital, Christchurch

Catheter related sepsis and suspected catheter infections are a frequent source of morbidity among haematology patients undergoing intensive chemotherapy. Immune suppression related to the disease process or cyotoxic therapy is one of the main risk factors for infection in this group of patients. These infections can be life threatening and a potential source for these infections are the present of an intravascular catheter. Although catheter related sepsis is only confirmed in a small number of patients a significant number of patients will have their catheter removed because of a suspicion of a central line infection. 80% of these catheters removed will be sterile when cultured after removal. Intravascular catheters are a “life line” for haematology patients, any method that helps maintain their patency and prolongs the catheter’s life without compromising its ability to be able to function has to be an advantage to our patients. FAS brushing is a recent development which can allow for early detection of infected indwelling catheters leading to more targeted and effective treatment regimen. This diagnostic tool may give the medical staff more confidence to leave a catheter *insitu* while continuing to treat a patient for a PUO in the setting of neutropenia. The FAS brush is inserted into the lumen of the central intravascular catheter to within 2cm from the end. As the brush is pulled back through the catheter lumen the debris within the lumen is removed including any bacteria and clots. This will be the first use of this brush in an immunocompromised patient group within Haematology.

134

Its Bleeding Obvious - not!!

Davis KG, Lucchesi G, Williams I, Hague S
State Blood Group Reference Laboratory, Transfusion Medicine Unit, IMVS, Adelaide

Blood group reference laboratories deal with a range of requests from simple investigations to the more complex and difficult, some of which test the resources and expertise of the staff involved. On occasions these difficult cases can have unexpected answers and in some adverse outcomes. In cases of rare findings, international co-operation may also be called upon. Two case studies will be presented, both of which called on the expertise and knowledge of the staff involved. Case 1: A now 36yr old female of Caucasian decent, first seen by us in 1992 [?anti-Jka]. Again in 1999 at end of fifth pregnancy [probable antibody to high frequency antigen - unspecified], neonate clinically unaffected. Then again in March 2003, at 30 weeks gestation in sixth pregnancy, with a suspected placental abruption, again all panel cells tested gave positive reactions. Extended testing against rare frozen cells also failed to provide an answer. Case referred to ARCBS NSW red cell reference laboratory for assistance, which was able to provide an answer. At 36 weeks three units of whole blood were sourced internationally to cover planned induced labour, which was uneventful. Neonate again had only mild transient jaundice. Case 2: An urgent request to provide compatible red cells for a 75 year old female post surgery for an aortic arch repair. On testing all panel cells were reactive and initial attempts to even provide 'crossmatch compatible' units were unsuccessful. Patient died shortly after request received. Due to some observed discrepancies in the testing of this initial sample, the pretransfusion sample was requested from the referring laboratory. Extensive testing over several days, including the eventual retrieval of historical data, provided a solution to this complicated case.

134

Identification of Antibody Mixtures

Ford DS
Immunohaematology Consultation & Education Services, Port Macquarie, Australia

When a patient's serum is found to be incompatible with all units crossmatched and to react with all panel cells, it presents a considerable problem to the blood bank staff that often needs solving urgently. The cause may be that the patient has developed an immune antibody to a high-incidence antigen lacking from the patient's red cells. If this is the case, the resolution of the problem will probably require the expertise of a blood group reference laboratory, which has access to many rare donor samples. However, more often, the problem is due to more easily solved causes, such as the presence of alloantibody mixtures or autoantibodies. Antibody mixtures can often be resolved in a routine hospital or private laboratory, using relatively simple techniques and inexpensive reagents. The only valuable commodity required is time! Methods that can be employed range from the very simple dilution of the patient's serum, through the use of multiple techniques and neutralization, to the more complex absorption/elution procedures. If the patient has not been recently transfused, genotyping of his/her red cells may provide valuable information on red cell phenotype. The recent trend to simplification of routine techniques due to the introduction of column-agglutination technology has resulted in newer staff having never been taught some of the basic methods for identification of antibody mixtures. This presentation will review those that are well within the capability of most routine blood bank laboratories, including the use of enzymes, neutralizing and inactivating fluids and absorption/elution techniques. The reaction characteristics of the various blood group antigens also need to be known, as these will often yield a vital clue.

146

French Haemovigilance Network Organization and Results: 1999 – 2002

Rebibo D, Hauser L, Herve P
EFS Headquarter – Medical and scientific Direction, Paris, France

Context: Haemovigilance, as defined in France by the law of 4th January 1993, represents a surveillance and alert system, from the blood collection of donors, to the follow up of recipients. It enables to collect and study the incidents occurring while using blood components (BC), in order to prevent their recurrences. Objectives: The French National Blood Service (EFS) gathers transfusion incidents on a national level. On a legal way, all the transfusion incidents reports (TIR) must be sent to both the EFS and the French Control Authority on Health Products (AFSSAPS). Method: From 1st January 1999 to 31st December 2002, all the TIR have been studied and analysed in order to improve their understanding and their prevention. Results: During the study period among the 30 954 transfusion incidents declared, 13 448 with strong transfusion imputability were specially analysed (60,3% immediate and 39,7% delayed incidents). The main causes of immediate incidents were allergy (48,3%), unknown (28,3%), immunologic incompatibility (12,3%) and less often, volemic overload and bacterial contamination. The delayed incidents were principally red cell immunizations (94,8%) but also viral contaminations (5,2%). For most of these, the transfusions were done previously to donors screening test and a very few after recent transfusions with donation in the window period. 914 suspicions of transfusion incidents related to bacterial contamination (TRBC) were declared and 57 confirmed cases analysed, among them 46 positive BC cultures. More than 50 % of the bacteria discovered in platelet concentrates with positive cultures were staphylococcus. The cause of BC contamination could be identified only in 4 cases. The occurrence of TRBC was

1/215 000 for all kind of BC and more important with platelets (1/25 000) than for RCC (1/510 000). The prevention's strategy is under consideration in France. 111 incidents with ABO incompatibility were notified. The primary source of error was clinical wards in hospitals (80%), in blood centres (15%) and 5% in particular cases. The occurrence for ABO incompatibility was 1/90 000. Among the 168 deaths notified in a transfusion context, 29 were real transfusion - associated fatalities cases : volemic overload (38%), immunologic incompatibility (34%), BC bacterial contamination (14%) ; and less often viral or parasite contaminations, allergy, and diverse (3,5%). The occurrence for death was 1/345 000 BC.
Conclusion: In France, since 1994, in addition to being an alert system, haemovigilance contributes strongly to transfusion safety. The next step according to the European Directive for transfusion will be the report on a national level of the donor's incidents.

147

A National Strategy for Optimal use in Ireland – what worked and what didn't

Murphy WG
Irish Blood Transfusion Service, Dublin

The Anti-D disaster of the mid-90s in Ireland brought blood transfusion to national prominence, and gave rise to several programmes and initiatives aimed at ensuring that blood and blood products were used appropriately at hospital level. There were three main approaches – the Haemovigilance programme, the National Blood Users Group, and the National Blood Strategy Implementation Group. Of these the Haemovigilance programme has been the most successful. Fully funded from the beginning, with a statutory basis and oversight by the National Regulatory Authority, it has been well resourced and co-ordinated. By grafting elements of the SHOT scheme on to the French approach of having haemovigilance officers in every hospital, a situation was rapidly achieved where a dedicated, recognised clinical blood transfusion resource, almost invariably a registered nurse, was available in each hospital. With good central support based at the BTS, but separate from its management and corporate structures, an active networking approach between the professionals, and fairly widespread acceptance at hospital level, the programme was able to achieve much more than adverse event monitoring and reporting. Haemovigilance nurses provide an invaluable resource for promulgating and implementing practice guidelines, and for systematic collection of transfusion data. The National Blood Users Group provides evidence-based guidelines for clinical practice. Appointed by the Minister and chaired by a Professor of Obstetrics, it consists mainly of hospital clinicians with some IBTS support. Inevitably, because there is no full-time staff member, the burden falls to one or two more or less enthusiastic individuals to keep it going. There is no reporting structure or oversight, and the task of co-ordinating a committee of geographically scattered and otherwise fully employed senior clinicians and the many working sub-committees is a thankless, difficult, and ultimately demoralising one. The National Blood Strategy Implementation Group was intended to oversee the implementation of optimal use defined through the Blood Users Group and the Haemovigilance process. Similar to the Blood Users Group, its members were appointed by the Minister and were drawn mainly from the hospital community. To date the impact of this group has been severely restrained, mainly by the usual complaint

that all involved have other jobs that are at least full-time. Overall vision, direction and co-ordination of these programmes is difficult to discern and changing personnel and priorities within the Department of Health pose a constant threat.

184

The South Australian Strategy - building a permanent commitment to quality and safety in transfusion practice in the health services of South Australia

Hetzel P[1], Robinson K[1]; Jones D[1], Davis K[2], Chapman P[3]
[1]Australian Red Cross Blood Service, Adelaide, [2]Institute of Medical & Veterinary Science, Adelaide, [3]Department of Human Services, SA Adelaide.

The Bloodsafe Project commenced in September 2002 and has proven to be a very successful collaborative activity between ARCBS, DHS and IMVS to establish quality assurance programs to improve the safety and quality of blood management practice within the South Australian health system. The Safety and Quality Council of the Department of Human Services approved the project funding for one year in the first instance. The strategy has been tailored for specific state purposes and includes 3 subprojects under the "Bloodsafe Project" banner and logo. The Bloodsafe name has guaranteed impartiality and acceptance by affected stakeholders, and as a result there has been significant collaboration of all institutions involved including hospitals and significant progress in introducing statewide initiatives and standard change has been possible. The structure of the project will be presented but includes 3 subprojects:

1. Appropriateness (effectiveness) of use in metropolitan public hospitals - incorporating the development of standard tools to measure (against NHMRC & ASBT guidelines) and interventions to ensure ongoing appropriate use. The emphasis of the project has been developing clinical partnerships with endusers at multiple levels at each hospital. Four transfusion safety nurse positions were appointed at Clinical Nurse Consultant level, usually from staff at the desired hospital. A specific background and experience working in haematology/oncology was required, and selection criteria specifically focussed on leadership and communication skills. A Bloodsafe Hospital Liaison Committee reporting to each hospital Transfusion Committee was established and provided a forum for project and hospital staff to review project outcomes.
2. Implementation of the ARCBS Haemovigilance program for measuring adverse and near miss events in the 5 South Australian Hospitals, has included initial safety audits of sample labelling, and interventions to improve performance standards. A patient interview proforma has been developed to assess patient satisfaction with the decision to transfuse in order to provide recommendations for the improvement of educational materials.
3. A Senior Project Officer who has significant experience in hospital transfusion laboratory management has undertaken the Review of Inventory Management in country areas. The activities have included mapping of formal and informal distribution networks and auditing of documentation procedures, & reviews of transport and packing. Standard documentation registers for managing component and blood product inventory have been developed and are being introduced where country hospitals lack electronic systems.

Highlights and key project success factors will be presented.

185

Defining Vein to Vein in New Zealand

Flanagan P
New Zealand Blood Service, Auckland

When NZBS was established in 1998 it promoted itself as a 'vein to vein' transfusion service. Whilst this approach has general support within New Zealand there is as yet no clear definition of what this should mean in terms of the overall development of the service. The initial energies of the NZBS have been devoted to the manufacturing aspects of modern transfusion. Increasingly however efforts are now been directed at the hospital blood banking sector and the clinical environment. If this approach is to be effective then it will be important that there is a clearly defined strategic framework to support initiatives to improve the overall practice of transfusion medicine. During the current financial year NZBS plans to undertake a consultation process to assist development of such a strategy. The consultation process will focus on three aspects of transfusion delivery. These are

1. The hospital blood banking function
   - Currently NZBS directly manages the hospital blood banks in 6 major hospitals. These are responsible for over 60% of blood components transfused in New Zealand.
   - The Progesa computer system will be in place at all DHB Blood Banks by the end of this year.
   - There is increasing pressure from IANZ for NZBS to provide oversight of the DHB Blood Banks.
   - What is the optimal configuration for future service delivery?
2. Clinical advice and support, including specialist services
   - NZBS efforts are curently focused on the larger DHBs.
   - How can a more comprehensive and more effective service be provided.
   - How can NZBS better integrate its activities across the sector
3. .Administration of blood and blood products
   - Haemovigilance data demonstrates that this is the area of greatest risk.
   - NZBS needs to establish its own model for haemovigilance
   - Nationally consistent policies might be appropriate but how to progress?

The key to success in promoting a vein to vein model for transfusion service delivery must be to work co-operatively across the health sector. This will not only facilitate implementation of 'best practice' initiatives but also enable a considered debate around the level of financial support available to achieve jointly agreed goals.

186

Modulating the Red Blood Cell (RBC) Membrane to Provide Universal/Stealth Donor RBCs Suitable For Transfusion

Garratty G
American Red Cross Blood Services, and University of California, Los Angeles, CA

Two approaches are being used to produce RBCs that can be used as "universal" donors (i.e., can be used for recipients of all ABO groups) or "stealth" RBCs that additionally will not react with non-ABO antibodies, and may be non-immunogenic. 1. Conversion of group A and B donors RBCs to group O by removing the terminal immunospecific sugar: We have known for more

than 50 years that group A and B RBCs could be converted to group O by cleaving N-acetylgalactosamine or galactose from the membrane of A and B RBCs respectively. In a series of studies 1980-1995, group B RBCs were converted to group O RBCs (ECO RBCs) using a coffee bean galactosidase, and successfully transfused to gibbons, human volunteers and finally, human patients. The first experiments used small volumes of ^{51}Cr-labelled RBCs and later experiments involved multiple transfusions of several units of ECO RBCs. RBC survival was normal and no clinical reactions observed. Problems were encountered with complete conversion of A RBCs to O RBCs using a chicken liver A-zyme. Newer sources of A-zymes are proving more successful, and the first clinical trials are due to start. 2. All RBC antigens can be camouflaged using polyethylene glycol (PEG). In 1977, pegylated proteins (PEG covalently bonded to proteins) were shown to have reduced immunogenicity and prolonged circulation in presensitized rats. It became popular to pegylate recombinant proteins used for therapy in humans. In 1996/1997, four groups tried independently to pegylate human RBCs. Such PEG-RBCs were found not to react in vitro with non-ABO antibodies (e.g., Rh) and ABO reactions were reduced but not prevented. Over the last five years, modifications of the PEG-RBCs have been produced in attempts to prevent ABO incompatibility (hemolysis, agglutination, sensitization detected by AGT and flow cytometry) and to overcome problems (e.g., non-specific RBC-bound IgG detectable by AGT, flow cytometry, and monocyte monolayer assays, suggesting clinical significance). Second generation PEG-RBCs have been produced that give very few of the above problems, but ABO still remains a problem. It is a possibility that a combination of ECO and PEG-RBCs may have to be used to produce a universal/stealth RBC suitable for transfusion. The most common cause of transfusion-associated fatality is transfusion of ABO incompatible blood. ECO or PEG-RBCs will prevent this, and PEG-RBCs (or ECO + PEG) will be invaluable for patients with autoantibodies and alloantibodies (e.g., multiple antibodies or antibodies to high incidence antigens).

187

Myelodysplastic Syndrome - A Review

Hudson PJ
ICPMR Westmead

Myelodysplasic syndrome (MDS) is a group of disorders characterised by bone marrow dysfunction. MDS are clonal stem cell disorders characterized by progressive cytopenia or cytopenias, usually in the presence of a hypercellular bone marrow and multi-lineage dysplasia. Usually, all three haematopoietic cell lines are involved. Mortality in MDS is related to bleeding, recurrent infection, and leukemic transformation. Bone marrow failure in MDS is due to ineffective hematopoiesis rather than a loss of hematopoiesis. In the absence of treatment, MDS can be a rapidly fatal disease. An estimated 20-40% of adults with MDS develop leukemia, and 30-40% of MDS patients succumb to infection, bleeding, or both. Therapy for MDS is often restricted to life long transfusion support, particularly in the elderly. Bone marrow transplantation remains the only cure for the disease. Because treatment for this group of patients involves regular transfusion, the incidence of red cell antibody detection is likely to be more frequent. Experience with this group of patients however, suggested that complex serological difficulties occur more often in MDS than in other groups of multi-transfused patients. Review: Patients from the geographical area of western Sydney that had been diagnosed with MDS by the Haematology department of the Institute of Clinical Pathology and Medical Research in the past 13 years were retrospectively identified by computer search. The laboratory serological and pre-transfusion testing records were reviewed for each patient identified. The data that was evaluated included:

1. The number of units transfused

2. The incidence and specificity of alloantibody/ies identified
3. The transfusion time interval prior to the development antibody
4. The incidence of autoantibody
5. Refractoriness to transfusion

188

Transfusion Medicine in a Developing Country – The Rewards and Heartaches

Devenish R, Eng S
Angkor Hospital for Children, Siem Reap, Cambodia

In developed countries the availability of many blood products is taken for granted. The same is not true for developing countries particularly Cambodia, which—after years of conflict—has one of the worst health systems in Southeast Asia. Working in Siem Reap, in the rural far north-west of Cambodia, the ongoing difficulty of keeping up with the demand for blood products, especially during the malarial and dengue fever seasons, is too familiar. Although blood donors are continually bled and tested, many are found to have positive hepatitis, syphilis or HIV serology. Since January 2001, when I volunteered to upgrade the laboratory at Angkor Hospital for Children, one of my main objectives has been to find ways of improving the supply and safety of blood products. When I first arrived the laboratory could only provide whole blood. Now, after a protracted, difficult process, the laboratory can make FFP. Further, the donation of triple donor bags from Terumo, has given us the resources we need to experiment in making cryoprecipitate for treating haemophiliacs and especially platelets so our leukaemic patients can be offered some form of treatment. When available, FFP saves many lives in acute situations. Though all too often, especially in the rainy season, the "cupboard is bare". Then, it is heartbreaking—to lose control of the haemorrhaging dengue patients and absolutely nothing remains for patients with chronic conditions such as haemophilia or nephrotic syndromes. The aim of my talk is evoke the experience of working at the "coal-face" of transfusion medicine in a developing country. I will describe the obstacles and how these were overcome and give you an insight into the rewards and daily dilemmas encountered in providing a safe blood transfusion service to the children at our hospital.

189

Can Volunteer Blood be a Commodity?

Whyte G

In the noughties, everybody expects that as much blood and blood products will be available as and when needed and at zero risk. However, without all our donors there would be no transfusion service to manage and many patients would die from blood loss, thrombocytopenia, haemophilia or hydrops fetalis. The Stephen Review acknowledged the importance of donors and expressed concern about the declining rates of volunteerism, but made no recommendations regarding donors. This discussion is about donors and volunteers and the power of social capital to effect change. Gift systems only survive with reciprocity. The opportunity for reciprocity when the return is delayed in time or removed in place or person, as in blood transfusion, requires a stable system and a managing agent that is trusted. In our complex societies, the stability of the system is managed through institutions where role is more important than person and through personal

networks. As in primitive societies, these systems can only be accessed by people who are empowered to do so. These social relationships can be referred to as 'social capital'. Informal initiatives eventually require institutionalization to be managed effectively. In fact, the conversion of home based activities such as eating or entertainment into service industries converts uncosted work into part of the gross domestic product. The work now becomes measurable in financial terms rather than social terms. In financial systems the manipulation of money, rather than the social process it represents, becomes the subject. This is often appropriate for commodities in order to drive the price down and availability up. However, financial measures are inappropriate for social goods, where the coinage is trust, group ownership and participation. When financial measures are applied to poor communities, their inability to respond effectively to challenges and opportunities are seen as failures, much as poverty used to be seen as a moral failure. In the case of blood, it is obviously important to sustain community trust in its safety and availability. But it should be central to the vision and operations of any blood service that the blood is only held in trust for the community. Blood services must use financial measures with caution because a focus on the dollar will distort the value of the gift and the social capital it represents. The blood services must, with the help of clinicians, manage the perceptions of their broader community and their funders that they are dealing with a gift with high social significance and not just a commodity.

197

Regulation of the Blood Products System – Viewpoint of a National Provider

Sher GD
Canadian Blood Services, Ottawa, Canada

Acting under the auspices of the Food and Drugs Act, the regulatory authority in Canada responsible for ensuring the safety, efficacy and quality of biologics and radiopharmaceuticals for human use, including blood and blood products, is the Health Products and Food Branch of the Federal Department of Health (Health Canada). Regulation has been applied to all sectors of the blood system, including fresh components, plasma and plasma derivatives since the late 1980s, prior to which the blood operator was essentially self-regulated in a culture of voluntary compliance. With the addition of "blood" to the list of drugs subject to the authority of the Food and Drug Regulations in 1989, mandatory standards began to be applied across the industry. The Krever Commission of Inquiry on the Blood System in Canada identified deficiencies in the regulatory oversight in Canada, and since then the regulatory environment has changed dramatically, and today is much more one of active, rather than passive regulation, within a maturing risk management framework. The Federal Government has enhanced the overall regulatory capacity for blood products since 1998, has sought independent expertise through a number of advisory committees, and continues to grow its laboratory research and surveillance capacities. There is extensive interaction with other regulatory authorities, and an ongoing effort at promoting harmonization across jurisdictions. From the perspective of the national provider, the changes brought to the regulatory environment, while welcomed and important, have not been without impact. This presentation will highlight these impacts and will address the need for clear accountabilities, transparent frameworks for decision-making, and open, effective dialogue between regulator and provider. This relationship is important to ensure the desired outcomes are achieved in terms of an appropriate balance between government regulation and voluntary industry standard setting and in terms of the regulator and provider working together to optimize product standardization while promoting innovations in safety and efficacy. In addition to regulating the blood provider, and ensuring compliance and enforcement of regulations through issuance of an Establishment License, Health Canada has developed Blood Safety Standards for Canada, which will take compliance requirements beyond the national operator, to hospital blood

banks and transfusion services. Regulation of the blood products system in Canada has changed dramatically over the past decade, and continues to evolve. This presentation will address the far-reaching impacts this has on the national blood provider and the influence such regulatory evolution has on the provider's business *Transformation*.

198

Regulation of Haemopoietic Stem Cell Delivery – viewpoint of a clinical transplant unit

Szer J[1]
[1]Bone Marrow Transplant Service, The Royal Melbourne Hospital, Australia

Increasing regulatory control has resulted in progressively more arduous documentation requirements, procedural rigidity and in many cases, the denigration of the value of creating individual solutions to unique problems. The underlying justification for such regulations has been the presumption that risk minimisation will result from adherence to guidelines and conversely, that failure to adhere to or failure to enact guidelines will introduce an unacceptable level of risk. Such risk may be clinical risk to patients or legal risk to institutions, professionals or authorities. Procedural guidelines have been of great value in ensuring that minimal standards of practice are being maintained and are intimately tied up in the process of accreditation of centres for various disciplines. Various authors have both extolled the virtue of guidelines and decried the negative impact on creative thinking such guidelines introduce. Guidelines and indeed regulations which insist on procedures that require the use of a particular product have the potential to breed "thought police" acting on behalf of the company owning the product and interfering with the clinical process.[1] Nevertheless, appropriate standards of practice combined with an accreditation process managed by professional peers are essential for maintenance of standards. The regulation of aspects of haemopoietic stem cell transplantation runs the risk of, at great expense, repairing a process that is not broken and possibly inducing breaks where none previously existed. Defining risks of adverse outcomes in the management of stem cells is a clinical rather than a regulatory responsibility. It is simple to demonstrate that improvements in outcome of patients undergoing stem cell transplantation have come about as a result of well-conducted clinical and preclinical research rather than regulation. The contribution of registries to outcome monitoring has been of particular value in this clinical and preclinical research rather than any aspect of regulation. The contribution of registries to outcome monitoring has been of particular value in such improvement. Clinicians regard the imposition of regulations at TGA levels as being resource-intensive and in general, a barrier rather than an adjunct to process improvement. The inevitability of such changes is well recognised however and providing appropriate resources are made available, most will comply rather than risk denying patients appropriate therapy.

199

Alloimmune Thrombocytopenia

Burrows R
[1]Monash University, Department of Obstetrics and Gynaecology 246 Clayton Road, Clayton, 3168, Melbourne, Australia

Alloimmune thrombocytopenia (AIT) is a complex disease involving the pregnant mother but affecting both the fetus and the newborn. Analogous to Rh disease the fetal has an antigen, this time on the platelet, which mother doesn't and thus mother mounts an immune response creating IgG antibodies which cross the placenta readily causing severe fetus thrombocytopenia. Unlike Rh disease, in AIT the first pregnancy is often affected. Increasingly, AIT has been recognised as

a major cause of haemorrhagic morbidity and mortality in fetuses and newborns. There are at least 16 antigen incompatibilities now identified; however, $P1^{A1}$ (HPA-1A) incompatibility results in the most severe thrombocytopenia and accounts for the greatest number of cases of intracranial haemorrhage (ICH), many of which occur antenatally. These cases are particularly significant because they occur in otherwise well, term newborns or even in fetuses. Studies in HPA-1A patients in subsequent pregnancies after the identification of an affected newborn in a previous pregnancy, have shown that fetal thrombocytopenia is typically both more severe and earlier in onset in the gestation. Incompatibility is usually identified by the birth of an apparently well fetus who develops signs and symptoms of severe isolated thrombocytopenia. The thrombocytopenia at presentation is typically $<10x10^9$/L and presents with petechiae, gastrointestinal, renal or intracranial bleeding. Mother is typically asymptomatic, having a normal platelet count and without evidence of recent viral infections. The diagnosis is confirmed by the demonstration of platelet antigen incompatibility between mother and partner ± antibodies to the antigen in the mother. Subsequent pregnancy management is problematic. The main stay of therapy is IVIgG however, corticosteroids, repeated cordocentesis and repeated intrauterine platelet transfusions are often required in selected cases. Platelet transfusions must be antigen negative and possess serologically negative HIV and CMV status. The platelets are washed and radiated prior to transfusion. The usual source of platelets are either the mother or a known antigen-negative donor. This presentation provides an update of AIT. It includes consideration of the clinical and laboratory diagnosis of the affected newborn as well as possible management strategies of both the affected newborn and the subsequent pregnancy.

200

Is a National Screening Programme for NAITP a Good Buy for the Health Care Dollar?

Murphy WG

Irish Blood Transfusion Service, Dublin

Several studies indicate that HPA1b/1a feto-maternal mismatches occur in approximately 2 percent of pregnancies in Caucasian populations, (range 1.6-2.5 percent) with fetal thrombocytopenia arising in nearly 1 in 1,000 live births. Most fetal or neonatal morbidity caused by maternal anti-HPA1a is mild, but neurological dysfunction or perinatal death has been recorded at a rate of approximately 1 in 10,000 live births, though in few studies. Long-term disease burden of brain-damaged infants has not been quantified, and the overall contribution of NAITP to the costs of care for neurologically dysfunctional individuals has never been assessed. Antenatal screening for NAITP may influence the natural history of the disease through early diagnosis of NAITP. However, there are as yet no useful predictors of disease in screen-positive pregnancies; combined with a serious complication rate of 1% or more per procedure for invasive fetal platelet counting this seriously limits the utility of screening at present. Because of the availability of routine ante-natal blood testing for rhesus haemolytic disease, screening for HPA1b status of pregnant women could be grafted onto an existing infrastructure, limiting costs to additional reagents and labour. Confirmatory testing, antibody screening, counselling and follow-up would be required for the 2% of pregnant women identified as HPA1b/1b. Costing initial screening at €4.10 per test we calculate the total yearly cost for 50,000 live births per year, including confirmatory testing, counselling and administrative costs at €400,000. Even if this resulted in averting only one severe case every five years the cost per quality of life year gained is acceptable at €30,000. In addition, the savings in costs of care for long term neurological disability would offset a considerable proportion of these costs: at a conservative estimate of €25,000 p.a. for residential care for 35 years per seriously affected child, preventing one severe case per year would completely offset the costs of a screening programme. Large scale studies

are required to identify whether screening for NAITP achieves real benefits in fetal outcome; however from a health economic point of view even a very modest benefit, which might realistically be achieved at present, NAITP screening merits very serious consideration. Furthermore, without the development of large scale studies involving hundreds of thousands of pregnancies (which can be justified at present) it will not be possible to develop effective antenatal interventions in screened at risk pregnancies.

205

Precautionism in Blood Safety Regulation - an irreversible trend?

Farrugia A
Office of Devices, Blood and Tissues, Therapeutic Goods Administration, ACT, Australia

Public and political expectations on blood safety are very high. This necessarily influences decision making, including the approach taken by regulatory authorities and other agencies charged with ensuring blood safety. Over the 1990's, several judicial or semi-judicial processes overseeing areas of transfusion practice where system failures resulted in viral transmissions invoked the "precautionary principle" as a philosophical tenet in blood safety. This principle, originally developed to assist in addressing environmental risks, increases the ability of decision makers to take steps to mitigate potential risks to the blood supply in the absence of conclusive scientific information regarding the nature or extent of the risk. The assimilation of the principle into blood policy decision making has been remarkable in rapidity and extent. Decision makers have also been liberal in their interpretation of the original principle and it is tempting to arrive at the impression that precautionism has become the ideology of conservatism in blood policy decision making. Coupled with the precautionist trend, a parallel pressure for cost-effectiveness and evidence-based decision making is generating an interesting tension between the two philosophies. In this presentation I will discuss the way in which precautionism, initially used as a justifiable approach to addressing a clearly inadequate decision making framework, has evolved into its current status as a major potential impediment to good practice in transfusion medicine. Such an analysis would lack value if it is not accompanied by an alternative approach, and I will propose that a synthesis between the two trends described should provide a rational way forward in the difficult environment which constitutes blood safety.

210

A Comparative Study to Determine the Efficacy of Using a Protocol of Routine Vital Signs Observations for Patients Receiving a Blood Transfusion

Thorp D[1], FitzGerald M[2], McCutcheon H[3], Davis K[4], Hodgkinson B[3], Athanasiadis K[3]
[1]ARCBS-SA, Adelaide, [2]Newcastle University, Newcastle, [3] University of Adelaide, Adelaide, [4]Institute of Medical and Veterinary Science, Adelaide

A study to determine the efficacy of vital sign monitoring during a blood transfusion was undertaken in a large tertiary referral hospital in Australia. The research was motivated by a lack of robust evidence to support vital signs protocols and the implications of routine monitoring to nursing time and patient comfort. Data were collected from cancer services and medical wards in a three-phase study. The areas acted as their own control and treatment group in a ‘before and after’ design. Inclusion criteria for participants were all adult patients admitted to the participating areas receiving a transfusion of packed red cell. Research assistants collected the data from all participants on age, gender, diagnosis, type of transfusion, number of units given and duration. The frequency of

variations in vital signs that elicited an action and the action taken were documented. Typical actions were to increase the frequency of observations, report to a doctor, change a transfusion rate, administer an antipyretic or antihistamine, consult with a senior nurse or stop the transfusion. Stage one (control) patients had routine observations as per the hospital protocol. Nurses knew of the study, but were not given any instructions to change practice.

Stage 1 (n = 475)	Compliance with hospital protocol	Action taken
Cancer wards	1.4% (1/144)	4.9% (7/144)
Medical ward	2.4% (8/331)	12.1% (40/331)

Stage two was a lead-in period to change practice from routine observations to observations prescribed at the discretion of the registered nurse. Nursing staff of the participating wards were given training sessions that included information about the study, blood transfusions and possible side effects or complications; professional roles and responsibility and decision making. Stage three was the treatment phase. All adult patients who consented had observations undertaken when the nurse assigned to their care, using professional judgement, considered vital signs measurement to be clinically indicated.

Stage 3 (n = 487)	Compliance with individualized protocol	Action taken
Cancer wards	64.5% (214/332)	5.7% (19/332)
Medical ward	36.8% (57/155)	10.3% (16/155)

This study demonstrates that the practice of routine vital signs observations was rarely followed. A similar number of actions were undertaken in each study group indicating that nurses were confident in deciding a clinically relevant vital signs observation protocol for their patients. Moreover, more nurses complied with their individual patient protocols than with routine hospital protocols.

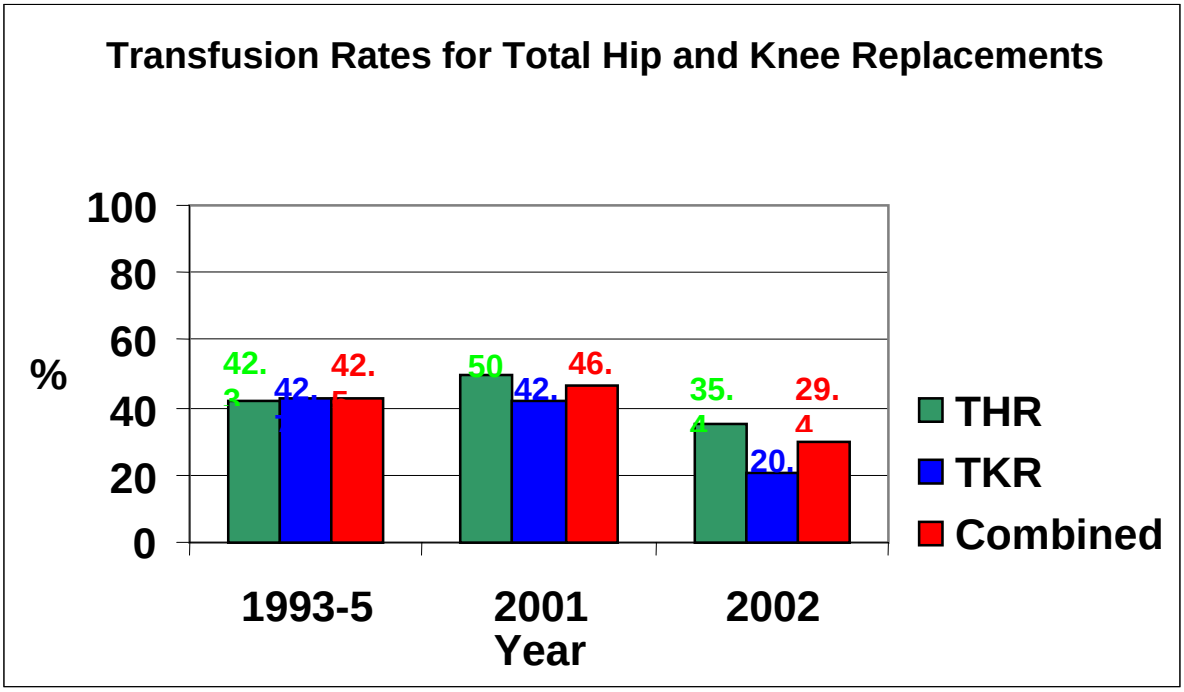
211

Using Audit to Reducing Allogenic Blood Transfusions to Elective Patients undergoing Hip and Knee Joint Replacements

Seigne RD[1], Chacko MDJ[1], Pereira RJ [1], Hodgson T[2]
[1]Anaesthetic Department, Christchurch Hospital, Christchurch, [2]Anaesthetic Department, Waikato

Background: Peri-operative transfusions account for 76% of allogenic blood transfusions in our hospital. Studies have shown up to 60% of allogenic transfusions are inappropriate in orthopaedic patients. Inappropriate transfusions put patients at risk of a range of undesirable outcomes. We audited the appropriateness and percentage of patients receiving allogenic blood transfusions in patients undergoing primary elective total hip joint replacements (THR) and total knee replacements (TKR). Subsequently, we introduced changes and re-audited our practice.
Methods: In 2001 227 consecutive patients were audited, 140 THR and 87 TKR using a data sheet completed during admission and later by note review if incomplete.
Subsequently the changes (below) were introduced.

1. Transfusion guidelines/triggers
"Allogenic blood transfusion is not recommended unless:
a) Haemoglobin concentration <80 g/l in a healthy patient or <100 g/l inpatients with cardio-respiratory disease.
b) There are signs/symptoms of anaemia +/- hypovolaemia or ongoing haemorrhage."
2. The use of post-operative autologous drains (POADs) was introduced for patients undergoing THR and TKR.
3. Staff were educated as to the rational behind these changes.
In 2002 a re-audit of 102 patients, 59 THR and 43 TKR, were performed. This audit also examined the efficacy of the three POADs used in the Orthopaedic Unit. Results: Variables likely to affect transfusion rates, pre-operative haemoglobin concentrations and patients' weight, were not significantly different between audit groups. The 2001 audit demonstrated a combined allogenic blood transfusion rate of 46.3%, THR 50% and TKR 40.2%. These rates were higher than those found in a previous audit in 1993-5. Following the introduction of the changes described above a re-audit was performed in 2002. The combined transfusion rate had reduced to 29.4%, THR 35.4%, 20.9% TKR.
Graph. Transfusion rates for THR and TKR and combined rates



The re-audit also demonstrated up to 41% of allogenic units transfused were not within the transfusion guidelines. It demonstrated POADs were not being used efficiently, 40% of patients did not receive blood collected in the drains. The Orthopaedic Unit's outcome audit recorded no change in post-operative complication rate.

212

Haemolytic Anaemia associated with Haemopoietic Cell Chimerism after Liver Transplantation

Webster B[1], Lammi A[1], Curtin J[1], Ogg M[1], Stormon M[2]
[1]Haematology & [2]Gastroenterology Departments, Royal Alexandra Hospital for Children, Westmead, Sydney. NSW. Australia

This case report documents the progress of a 9 year old girl, Group O Rh (D) Negative, admitted in fulminant liver failure of unknown aetiology. She underwent successful liver transplantation from an un-related, Group O Rh (D) positive male donor who was not HLA identical. Nine months post-transplant the recipient's blood group was found to have converted to Rh (D) positive. Over the next four weeks the girl developed a Coombs Positive Haemolytic anaemia (IgG & C3d coating). Her blood film showed intense red cell spherocytosis. Severe anaemia with periods of intravascular haemolysis with haemoglobinuria persisted for the next 3 months. The patient required frequent red cell transfusions and did not respond to high dose prednisone, intravenous gamma globulin or changing the post-liver transplant immunosuppressive therapy from Tacrolimus to cyclosporin. Proof of haemopoietic stem cell chimerism was obtained twelve months post-transplant with fluorescent in-situ hybridisation (FISH) studies using DYZ1 as a Y chromosome and CEPX as an X chromosome marker. Bone marrow myelod, erythroid and CD19 positive B cells were all XY; (50 cells analyzed). Peripheral blood lymphocyte subsets were interpreted as showing B cells to be 98% male, 2% female; T cells to be 94% male, 6% female while NK cells were 100% male. It seemed likely that the haemolytic anaemia was the result of the girl's remaining lymphocytes mounting an immune response against the engrafted donor erythroid cells. Cyclosporin therapy was ceased and the prednisone dose gradually reduced over three months. The anaemia and reticulocytosis; completely resolved. Haemoglobin levels continue to be normal six months after ceasing all immunosuppressive therapy. The direct antiglobulin test is currently weakly positive with IgG coating antibody. Repeat FISH analysis on peripheral blood cells 20 months post-transplant showed granulocytes, T & B lymphocytes were all XY. Micro-chimerism in paediatric liver transplantation has been previously documented in both early and late follow-up studies utilizing polymerase chain reaction for HLA sequences. Complete multilineage donor haemopoietic cell engraftment has previously been reported in an adult liver transplant recipient who received massive immunosuppresive therapy for treatment of Graft versus Host disease. This report documents haemopoietic engraftment complicated by haemolytic anaemia in a child maintained after liver transplantation on standard immunosuppression.

213

Review of Positive Direct Antiglobulin Tests Found on Cord Blood Sampling

Dinesh D
New Zealand Blood Service, Wellington

Background and objective: Until recently, all babies born in Wellington had umbilical cord blood sampling for direct antiglobulin test (DAT). It is considered to be an important test in identifying babies who are at risk of haemolytic disease of the newborn (HDN) due to ABO incompatibility. The purpose of this review was to examine the utility of positive DAT results and ascertain

- How many cases required phototherapy?

- Were any babies readmitted for phototherapy?
- Did the positive DAT influence the detection and treatment of HDN?

Methods: The clinical records of all newborn babies found to have positive DATs by Wellington Hospital Blood Bank, over a 6 month period (January – June 2001) were reviewed. Results: A total of 94 babies with positive DATs were identified. 22 of the 94 (23%) received phototherapy. 6/22 (27%) of those babies that received phototherapy were alerted by a positive DAT, leading to measurement of serum bilirubin (SBR). 12/22 (55%) were initially alerted by clinical jaundice, leading to measurement of SBR. 2/22 (9%) were discharged and readmitted (on Day 3 and Day 5) for phototherapy. 1 of these babies had the positive DAT documented and a history of siblings who had received phototherapy for HDN. 2/22 (9%) were diagnosed antenatally (both anti-D HDN). 1 baby received an exchange transfusion in addition to phototherapy. 2 babies that received phototherapy had SBRs in the exchange transfusion range. 86% of the cases of HDN treated with phototherapy were due to anti-A. 41 of the 72 cases (57%) that did not receive phototherapy had no documentation of the positive DAT result in the clinical notes. Conclusions: Approximately a quarter of the babies with positive DATs received phototherapy for HDN. 2 babies required readmission for phototherapy, on Day 3 and Day 5. Jaundice rather than the positive DAT was the first alert in the majority of cases of HDN requiring phototherapy.

214

TRALI – rare but potentially under recognised complication of childhood transfusion

Fung Y[1], Williams B[2]

[1]Australian Red Cross Blood Service, Queensland, Brisbane, [2]Royal Children's Hospital, Herston, Brisbane

TRALI: Transfusion-related acute lung injury (TRALI) is the third most common cause of fatal transfusion reactions. It is characterised by acute respiratory distress, acute pulmonary infiltrates and hypoxemia occurring within 6 hours of commencing a transfusion. TRALI has been reported to occur 1 in 1323 units transfused. This contrast significantly with the 1 in 40,000 units transfused incidence in Queensland, Australia (calculated over a 27 month period). This suggests that TRALI is significantly under recognised and therefore under reported and under investigated in Australia. Case: TRALI has been rarely described in children. This report documents a case of TRALI in a 2 year old female with Downs Syndrome and AML. The child was on Voraconazole for a chronic fungal infection. She presented with pancytopenia intercurrent neutropenic sepsis manifesting with fever but no localised infection. Her severe thrombocytopenia necessitated transfusion of 4 units of leucocyte depleted irradiated single donor platelets. When the transfusion was almost complete she developed fever, cyanosis and cutaneous mottling. She was hypotensive, tachycardic and hypoxic with an oximetry saturation of approx 80%. The transfusion was ceased and she was treated with oxygen and received 2 doses of frusemide. She improved gradually over 3 to 4 hours with improvement in oxygen saturation to 90-92%. Results: Neutrophil antibodies were not detected in the patient and serum from 3 out of the 4 platelet donors. In a neutrophil cross-match these 3 platelet donors were compatible with the patient's neutrophils. Anti-HLA antibodies was detected in the 4th platelet donor and in the cross-match this donor's serum was not compatible with the patient's neutrophils. Summary: The positive cross match between patient neutrophils and donor serum provides important laboratory evidence in support of the initial clinical diagnosis of TRALI. The identification of the "culprit" donation is

critical in haemovigilence as single donors have been linked to multiple TRALI reaction. It enables the blood service to identify the responsible donor and bar their blood products from ever being used for therapeutic purposes, thus reducing the incidence of this serious transfusion reaction.

215

Transfusion Protocols for Congenital Chronic Anaemia Patients

Tompson E[1], Davison T[1], Wong J[1], Hyland C[1], Williams B[2], Davis K[3]
[1]Australian Red Cross Blood Service – Brisbane, [2]Royal Brisbane Hospital – Brisbane, [3]IMVS – Adelaide

This study was designed to identify current practice for the selection of red cell products for patients with congenital anaemia requiring frequent long term transfusion support. The information was gathered using a confidential survey distributed to medical institutions via the Australian & New Zealand Society for Blood Transfusion and participants in the Royal College of Pathologists Australia Immunohaematology Quality Assurance Program. The survey consisted of 12 questions relating to red cell selection for these patients. Approximately 765 surveys were sent to 339 institutions, with an institutional return rate of 24% showing the following results:

- 38% of the respondents treated congenital chronic anaemia patients and of these
- 16% treated >50 patients
- 10% treated 25-50 patients
- 48% treated <25 patients and
- 26% did not specify the number of patients treated.

Approximately 597 patients are treated for congenital chronic anaemia at the institutions that responded and comprise the following:

- 1% Alpha Thalassemia
- 48% Beta Thalassemia
- 2% Sickle Cell Anaemia
- 2% Sickle Cell Thalassemia
- 2% Diamond Blackfan
- 9% Other anaemias eg. Hereditary Spherocytosis, Paroxysmal Nocturnal Haemoglobinaemia, Congenital Dyserythropoetic Anaemia and Myelodysplasia
- 37% Unspecified anaemia.

The following criteria are used when selecting and transfusing blood products:

- 48 % transfuse group specific, crossmatch compatible
- 42% phenotype patients at diagnosis
- 39% transfuse phenotypically matched
- 32% transfuse antigen negative blood in the absence of red cell antibodies.
- 35% transfuse fresh blood (range 1 – 14 days)
- 32% transfuse pre-storage filtered red cells
- 32% transfuse bed side filtered red cells
- 19% transfuse washed red cells
- 66% indicated they would consider using pre-storage filtered red cells if there was no other clinical need for washed cells.

The respondents indicated that the following parameters were used to measure the requirement and/or effectiveness of transfusion:

- 48% use pre-transfusion haemoglobin levels

- 3% use post-transfusion haemoglobin levels
- 35% use both pre-transfusion and post-transfusion haemoglobin levels
- 13% use other methods.

The minimum pre-transfusion 'trigger' level of haemoglobin used to determine the need for transfusion varies considerably between institutions:

- 10% use a trigger of 51-75g/L
- 35% use a trigger of 76-90g/L
- 32% use a trigger of 91-100g/L
- 3% use a trigger of 101-110g/L
- 19% use an alternative trigger.

Haemoglobin 'triggers' are the most commonly used parameters for monitoring effectiveness of transfusion with the desired post-transfusion haemoglobin level ranging from 100 to 140g/L among the respondents. The majority of respondents indicated that most of these patients require monthly transfusions. This study demonstrates the extreme institutional variation in transfusion protocols for patients with congenital chronic anaemias. . The low response rate probably indicates that treatment of these patients occurs at specialist centres. It is interesting to note that only 35% of respondents appear to consider the age of the product to be important. The development of guidelines for the selection of blood products for these patients may be of value in enhancing their quality of life.

216

Human Monoclonal Antibodies Specific for Epitopes on RhD Antigen

Yuan FF, Watt JM, Suarez M, Biffin S, Sullivan JS
Australian Red Cross Blood Service-Endeavour, Sydney, Australia

The D antigen is one of the most immunogenic of human red cell antigens in spite of its relatively low number of antigen sites per cells. The D antigen is also known to consist of a mosaic of epitopes [1]. The initial classification of the D antigen into 7 categories was based on the reactivity of D-positive red cells with monoclonal anti-D[2]. By studying serological profiles of specific monoclonal anti-D against D variant red cells, many additional D epitopes have been described [3,4]. More recently, by analysing the molecular bases of some D variants, six different epitope clusters have been reported [5]. In this study, we analysed six in house human IgM monoclonal anti-D against the D category/variant cells (IIIa, IIIb, IIIc, IVb, Va, VI, VII, DFR, DBT, DNU, DOL, Del and R_0^{Har} etc.). Three patterns of reactivity were observed: one anti-D (2A9/2E7) recognised epitope 18 or 33, two (3B11/1F7 and 3B11/2D6) recognised epitope 34 or 35 and other three (4F5/1F9, 4F5/1G11 and 4F5/1G12) recognised epitope 10 or 11. Those monoclonal anti-D were shown to be suitable for use in blood grouping /phenotyping reagents as well as for the epitope studies. Together with other in house monoclonal anti-D [4,6], a panel of monoclonal anti-D can be set up to determine D variants as well as blood grouping/phenotyping for clinical use. Further studies, in comparison of the serological data with mutagenesis of those D variants, will help us to understand molecular basis of the D epitopes.

217

Neonatal Anaemia Requiring Transfusion Associated with Anti-TSEN/MINY Antibodies Produced in Response to GpJL (MiXI) Incompatibility

Traino T[1], Tapp H[1], Chen W[2], Watt J[3], Davis A[3], Tocchetti E[4], Ward C[2] and Flower R[2]
[1]Women's and Children's Hospital, Adelaide, [2]Pacific Laboratory Medicine Services and University of Sydney, Sydney, [3]Blood Group Reference Laboratory, Australian Red Cross Blood Service, Sydney, [4]Red Cell Reference Laboratory, IMVS, Adelaide

Glycophorin JL (GpJL)(Mi.XI phenotype) is a GpA-B hybrid which expresses the S antigen and the low-incidence antigens of MNS system TSEN and MINY. The aim of this study was to investigate the serological basis of neonatal anaemia in an infant (DR) with a positive DAT and anaemia requiring several transfusions. Standard immunohaematological serology techniques were used and DNA amplification and sequencing were carried out using standard techniques with primers and conditions described elsewhere. ELISA was with biotinylated-peptides representing various Mi antigens captured by streptavidin conjugated to a plastic surface. The level of antibody (IgG) in a 1:10 dilution of serum was quantified by measurement of absorbance following incubation with HRP-protein-G and substrate. When serum from the mother of baby DR was investigated, no reaction was detected with cells used for routine screening but the mother's serum reacted with the father's red cells. When reacted with a panel of cells of various Miltenberger phenotypes the mother's serum reacted with cells expressing MINY or TSEN antigens. The father's red cells typed as S+s+, MINY+, Hil-,Mur- suggesting Mi.XI(GpJL). ABO compatible sera for TSEN typing were not available. Sequencing of PCR products amplified with primers for GPA from the exon 3 region and GPB from the exon 4 region of the father's glycophorin gene demonstrated an S-specific GP(A-B) hybrid coding for GpJL (MiXI). A crossover point in the intron between the GPA exon 3 and GPB exon 4 was identical in the father and the child but different from the initial propositus, evidence of a lineage for inheritance of GpJL in this family different from that for initial case. By peptide-ELISA the antibody from the mother reacted with a peptide representing the MINY antigen but not peptides representing Mi(a), Mur or Hop antigens. In summary, a foeto-maternal incompatibility due to GpJL (MiXI) resulted in production of anti-TSEN (antibodies that react with the GpA-B exon 3/4 junction combined with the S form of S/s polymorphism) and anti-MINY (antibodies that react with the GpA-B exon 3/4 junction that do not discriminate between S and s forms of the S/s polymorphism in exon 4 of GpB). Antibodies to variant glycophorins expressing low incidence antigens of the MNS system have been shown to cause haemolyic disease and anaemia in the newborn, however, this is the first report of severe neonatal anaemia requiring transfusion as a result of an incompatibility defined by GpJL.

218

Application of Molecular Genetic Techniques to Detection and Characterisation of Antibody to the Scianna 2 Polymorphism

Flower R[1], Toopran S[1,2], Kamhieh S[1,2], Ward C[1] and Bolton W[2]
[1]Pacific Laboratory Medicine Services and University of Sydney, Sydney, [2]Australian Red Cross Blood Service and University of Sydney, Sydney

In 2001, detection on the surface of erythrocytes of a previously undescribed 60 to 68 kD glycoprotein mapping at 1p34-36 was reported. As the size and location of this protein were the same as the Scianna protein it was likely that this glycoprotein was the carrier of the Scianna 1/2

(Sc1/2) polymorphism. In 2002 Wagner, Poole and Flegel reported that both the Sc1/2 polymorphism, G169A predicting a Gly57Arg substitution, and the Radin polymorphism are expressed on this erythrocyte membrane-associated protein (ERMAP). It has been reported previously that anti-Sc2 antibodies in an affected infant produced a positive a DAT and ongoing immune haemolysis requiring transfusion. This is one of several published examples of anti-Sc2 related haemolysis. The frequency and haemolytic potential of anti-Sc2 may be underestimated because it is not usual to further investigate DAT-positive infants when there is an ABO incompatibility and a negative maternal antibody screen. For 300 antenatal specimens for which no antibodies to red cell antigens had been detected by routine screening in a card antiglobulin test, screening was repeated with an Sc2 positive screening cell. Four anti-Sc2 antibodies were detected, three were weak (score 3) and one score 8-10. In none of these cases was presence of the antibody associated with an adverse post-natal outcome for this pregnancy. For sera from 170 donors, relative reactivity with Sc1 (SLWP**G**TVPK) and Sc2 (SLWP**R**TVPK) peptides was investigated by ELISA. Several sera that reacted preferentially with the Sc2 peptide did not agglutinate Sc2 positive cells in a card antiglobulin test, indicating that this test was not sufficiently specific to be useful in screening for anti-Sc2 antibodies. At concentrations in excess of 0.5 mg/ml some peptides incorporating the Sc2 polymorphism partially inhibited agglutination of Sc2-positive cells by anti-Sc2. Optimal conditions for demonstration of inhibition of agglutination are being investigated so that peptide-inhibition can be used to confirm the specificity of antibodies reacting with Sc2 positive cells. As antisera for Sc1/2 typing were not available, PCR-SSP for ERMAP alleles was used to genotype 170 donors. The primers used were those described by Wagner, Poole and Flegel, with nucleotides complementary to those specifying the G169A polymorphism at the end of the antisense primers. For two donors, products were amplified with both Sc1 and Sc2 specific primers, indicating a heterozygous Sc1/Sc2 genotype. Application of these molecular genetic techniques provides a basis for improved evaluation of the frequency and significance of anti-Sc2 related haemolytic events.

244

Blood Conservation: the 'hot topic' in medicine

Isbister, JP[1]
Royal North Shore Hospital, Sydney

Homologous blood component therapy has had a central role in the development and practice numerous medical and surgical advances. However, in recent years that blood transfusion is no longer regarded as essential for a wide range of disorders and most major surgery can now be conducted without the use of homologous blood. Stemming from the recognition that HIV could be transmitted by homologous transfusion there has been an increased awareness of the potential hazards of homologous blood components and a resurgence of interest in methods for minimising exposure. With the exception of chronic haemopoietic deficiencies, homologous blood transfusion is usually supportive therapy and is generally only required for until the basic disease process can be corrected. For most patients it is possible to minimise requirements for homologous blood components or to correct or manage the effects of deficiencies in the haematopoietic system without transfusing homologous blood components. Clearly, if homologous blood can be avoided the potential hazards need be not be considered. As with all modern medical therapy, blood component therapy presupposes an understanding disease in terms of pathophysiology, definition, classification, diagnosis, indicators of severity and prediction of the natural history of untreated and treated disease. With many clinical disorders where blood component therapy may have a role the disease or problem is well understood with

others our understanding can only be regarded as rudimentary. Modern transfusion medicine practice is now focusing more on the clinical problem (ie the question) rather than the blood component (ie the presumed answer). With this approach there is a more considered analysis of the risk-benefit equation for the transfusion of homologous blood components. Better understanding of pathophysiology, clinical trials to assess benefit, advances in near patient pathology testing and improvements in technological and pharmacological methods for minimising transfusion are all contributing to a major rethink of transfusion practices. We are now seeing the evolution of a blood management philosophy in clinical practice in contrast to transfusion management as the main focus.

246

Haematology and Transfusion Medicine's Perioperative Role in Blood Conservation

Leahy MF

Fremantle Hospital Perth

Introduction: Blood conservation is a global concept using strategies aimed at reducing exposure to allogeneic blood products. The transmission of infections such as HIV and Hepatitis C have increased public awareness of the adverse effects of homologous blood transfusion. Successful perioperative blood conservation involves an integrated approach to the management of surgical patients involving haematologists and transfusion medicine specialists. Aims: The aims of blood conservation are to optimise the preoperative red cell mass, minimise blood loss and optimise blood transfusion practice. Preoperative phase: In this phase the patient's fitness for operation is assessed. The haematological assessment includes drugs that may impair haemostasis, anaemia and any history of abnormal bleeding. Routine laboratory investigations such as FBC, clotting screen, iron studies, B12 and folate levels, renal and liver function are appropriate with more specific tests of coagulation and platelet function as necessary. Identification of specific haemostatic abnormalities such as von Willebrand's disease may require further investigation and assessment of response to therapeutic agents eg DDAVP. Maximising Haemopoiesis: Treatment with iron, oral or IV, B12 and Folate, if deficient or borderline, may lead to an increased red cell mass. Erythropoietin will raise the red cell mass in preparation for surgery but needs to be supplemented with iron for optimum response. This allows more intensive preoperative autologous blood donation, intraoperative haemodilution and more rapid postoperative haemoglobin recovery. Minimising blood loss: Careful anaesthetic and surgical planning and management is crucial in minimising blood loss during the operation. In situations where there is an increased risk of blood loss such as a previous history of operative blood loss without identifiable cause, in mild type 1 von Willebrand's disease, mild haemophilia and some disorders of platelet function DDAVP may enhance haemostasis. The antifibrinolytic agents tranexamic acid and epsilon – aminocaproic acid are useful perioperatively in mild bleeding disorders especially in dental and oral surgery and some orthopaedic operations. Postoperative phase: Continue blood loss minimisation techniques e.g. microsampling to reduce daily blood loss. Careful monitoring of coagulation parameters and management of blood loss is required. Optimise transfusion practice: The decision to transfuse is based upon clinical judgement taking into account the patient's physiological reserves and the likely risk of complications related to postoperative anaemia. Guidelines for transfusion need to

be regularly reviewed and kept up to date with evidence from clinical studies. Conclusion: An effective blood conservation strategy requires a multidisciplinary approach. Central to this is the leading role of haematology and transfusion medicine practice.

247

Liver Transplantation in a Thrombocytopenic Patient without Allogeneic Blood Support: lessons learned for broader blood conservation

House AK[1], Gibbs NM[2]

[1]West Australian Liver Transplant Unit, Sir Charles Gairdiner Hospital, Perth, [2]Sir Charles Gairdiner Hospital, Perth

Introduction: Improvements in blood conservation and surgical techniques have enabled surgeons, in many cases, to perform uncomplicated orthotopic liver transplantation (OLT) without the need for allogeneic red cells. However, other allogeneic products, such as fresh frozen plasma and platelets are often required to improve coagulation. Recently, the introduction of recombinant activated factor V11 (rV11a) has reduced reliance on allogeneic blood products and better preoperative preparation has reduced the need for blood transfusion. Aim: The objective was to provide a proactive clinical care programme that would allow OLT without giving allogeneic blood products. Methods: A 47 year old man with end stage liver disease secondary to alpha-1 antitrypsin deficiency was assessed for OLT. He had severe thrombocytopenia but otherwise normal coagulation function. He refused all allogenic blood products other than albumin and accepted the increased risk of peri-operative mortality. Pre-operative treatment with erythropoietin, iron, folic acid, vitamin B_{12}, intraoperative normovolaemic haemodilution, intra-intra-operative aprotinin, careful heamostasis, autologous red blood cell salvage were all used as bleeding control methods and rFV11a if required was available. Results: Pre-operatively his haemoglobin improved from 110gms/ (haematocrit 0.32) to 150 gms/l (haematocrit 0.46) and the platelet count remained unchanged at $55x10^9$/l. The uncomplicated procedure lasted 4hr 50 min with an estimated blood loss of 3000ml for which he received 3000ml crystalloid solution, 5000ml gelofusin, 800ml washed autologous cell-saved blood and 2 units of autologous blood collected at the start of the procedure. On admission to the intensive care unit (ICU) his Hb was 103 gm/l. Surgical haemostasis was secured despite a platelet count $59x10^9$/l, INR 3.2 and APPT 90. In ICU he received rV11a 3 treatments for his elevated INR but no further allogeneic blood products other than albumin. This outcome is compatible with other published data from units in the United States and United Kingdom who use similar bloodless surgical techniques. Conclusion: This case demonstrates the principle that OLT may be performed without the use of allogenic blood products, so long as the procedure is uncomplicated and blood loss is controlled. Recombinant FV11a is a major advance that reduces the reliance on allogeneic products to promote coagulation but even without using this medication in the thrombocytopenic patient careful preoperative management, haemodilution, scrupulous haemostasis and cell salvage enhance the ability to control blood loss.

254

Improving Blood Transfusion Safety: Education Interventions from the BloodSafe Project

Roffey T[1], Hunt R[2], Quested B[3], Verrall T[4], Davis K[3], Hetzel P[5], Thorp D[5], Robinson K[5]
[1]Queen Elizabeth Hospital, Adelaide, [2]Flinders Medical Centre, Adelaide, [3]Royal Adelaide Hospital, [4]Women's and Children's Hospital, Adelaide, [5]Australian Red Cross Blood Service-South Australia

BloodSafe is a state wide collaborative project sponsored by the South Australia Hospital Safety and Quality Council of the Department of Human Services and Australian Red Cross Blood Service-SA. The aim of the project is to improve blood transfusion safety and efficiency. This paper details the educational interventions undertaken by the BloodSafe group aimed at improving transfusion practice. Changes to individual institution policies and procedures were undertaken at each of the sites. However, the BloodSafe group identified the need for more unified policies and procedures and a common knowledge base to support best transfusion practice. Areas of concern identified by the group included compliance by staff with sample collection and labelling; correct handling and checking of blood products; and staff knowledge levels. A 30-minute in service education session for nurses was developed for use at all five campuses. These sessions started with nurses anonymously answering six questions that attempted to delineate gaps in knowledge. This helped to make nurses more receptive to the information that followed. Answers to the questions were then provided including a discussion of rationales for specific hospital practices in relation to blood transfusion. The video comedy "The strange case of Penny Allison" (NHS) that highlights transfusion issues was shown to participants to reinforce practice. Additional educational interventions were developed for other hospital staff groups e.g new overseas doctors. Posters reinforcing correct collection and labelling procedure were placed in key locations throughout the hospital. A checklist was developed detailing the correct step by step process for administering blood. Stickers with simple slogans promoting awareness of blood safety were devised and attached to a number of items including chocolate bars, patient folders, and equipment. Cards with the current risks of blood transfusion and the process of informed consent were developed. These were distributed to medical staff, and were also placed in pre-operative assessment areas for reference when consenting patients undergoing planned procedures. As a result of these interventions compliance with sample collection and labelling and awareness of correct handling of blood products by nursing staff has measurably improved. Staff at each of the intervention sites has a greater awareness of blood transfusion safety issues. The implementation of a state wide education program has produced identifiable improvement. Sustaining such an improvement will be an ongoing process.

255

Understanding the Value of a Blood Service from the Perspective of its Stakeholders

[1]Fletcher A, [2]Lavelle A, [3]Guthrie J, [3]Steane P, [4]Roos G
[1]Growing your Knowledge, Sydney, [2]Australian Red Cross Blood Service, Melbourne, [3]Macquarie Graduate School of Management, Macquarie University, Sydney, [4]Centre for Business Performance, Cranfield University, and [5]Intellectual Capital Services, London, United Kingdom

Not-for-profit organisations generally have multiple stakeholders making their management complex. Blood services whether in the public, private or not-for-profit sectors provide an essential public service and a fundamental 'public good' but are subject to intense public scrutiny. They face a challenge in balancing the needs of patients and the community, blood donors, hospitals/blood service users, their funding bodies and regulators. The Australian Red Cross Blood Service (ARCBS) was interested in gaining a better understanding of the value it held for its stakeholders. ARCBS undertook a study of stakeholder value collaboratively with the Macquarie Graduate School of Management and Intellectual Capital Services. The first outcome was to identify eleven major stakeholder groups as: Blood Donors, the Commonwealth Government of Australia, State and Territory Governments, the Red Cross Society, the Health Sector, the commercial Plasma Fractionator, Suppliers, R&D Institutions, various Regulators, the Media, Unions. Background research, internal input from ARCBS and information from overseas blood services was obtained to set the framework. A values hierarchy was developed, consisting of nine Key Performance Areas (KPAs) for ARCBS, by interviewing various stakeholders. The model was refined using an iterative process until it was inclusive of all stakeholder views. The researchers then surveyed a larger group of stakeholders who were asked to prioritise the KPAs and the 65 attributes of which the KPAs were comprised. Stakeholders were also asked to characterise the behaviour of the attributes and to decide if they should be considered as indispensable. Analysis of the results confirmed the accuracy of the hierarchy and revealed a common agreement of the four most highly valued KPAs as safe product, product sufficiency, donor and volunteer management and maintenance of public confidence. Other KPAs were R&D and other services, external, internal, and people management, and working with stakeholders. However, there were major differences between different stakeholder groups in their perceptions of the relative importance of the nine KPAs and their attributes. As a result of the study ARCBS has a better understanding of the stakeholder perceptions of its value. It is possible now for ARCBS to develop its organisational strategy, its performance management systems and to frame its communication with stakeholders on the basis of this knowledge. ARCBS has already undergone a restructure to better address stakeholder interests, partly in response to this study, and it is considering future strategies and options.

256

Patient's Experiences of Blood Transfusion

Corkery C
New Zealand Blood Service, Hamilton

Blood transfusion is a routine and safe procedure in hospitals in New Zealand. There have been several articles originating from New Zealand sources that cover the safety aspects of blood products given to New Zealand patients, however to the author's knowledge there has been no study to ascertain the views of New Zealand patients receiving fresh blood components. Since the establishment of NZBS, it has been a requirement that patients are to give informed consent before a blood product transfusion. Objective: This study's objectives were to ascertain whether patients gave informed consent for blood transfusion, if they were satisfied with the information they were given and what their experiences/concerns of the blood transfusion were. Method: using a modified version of a questionnaire by Gray & Murphy (1993), 201 (49 Maori, 147 European) patients at one large hospital in New Zealand were interviewed by the author. Interviews averaged 15-20 minutes in length and were conducted within 5 days of the transfusion. Patients who were in intensive care units, high dependency units, delivery suites, paediatric departments or emergency departments were excluded. Results: 72% (145) of patients interviewed had signed a consent form. However, 18% (27) of this group were not satisfied with the information they were given, suggesting that only 58% (118) of patients gave informed consent. Although 71% (144) of the patients were happy with the information they were given from clinicians, only 16% (33) of the patients could recall being given any written information. 26% (53) of patients had concerns about blood transfusions with viral infections being the most prominent worry for patients. Of those patients interviewed only 15% questioned the clinician. 93% of this group were satisfied with the answers received. Patients offered 330 comments with 55% being positive, 22% being negative and 23% were considered by the author as being neutral. There were no significant differences between Maori and European groups. Conclusion: in relative terms this study was a small one, however the results are still relevant to the practice of transfusion medicine in New Zealand. They provide a baseline of patient's perceptions towards blood transfusions and they indicate that a sizeable proportion of patients are not given enough information to alleviate their concerns or make an informed consent.

257

Isn't My Signature Enough? - aligning clinical decision making with the NHMRC blood component guidelines in the orthopaedic unit.

Aitken GL, O'Shea K, Beck T, McDonald H, De Silva R
Blood Matters Team, Royal Hobart Hospital, Hobart Tasmania

The release of the National Health Medical Research Council (NHMRC), Blood Component guidelines in 2001 was heralded with little impact at the Royal Hobart Hospital (RHH) on ordering of blood and blood products. In January 2003 RHH joined the Blood Matters Collaborative a Victorian Government initiative. This project revolves around the core concept of aligning clinical decision making with the NHMRC guidelines. The focus area for our study is the RHH Orthopaedic unit (ORU). A retrospective study of all transfusion in ORU was conducted for the financial year 2001-2002 prior to any education on the NHMRC guidelines. The Collaborative provided a

quantum of transfusion, a haemoglobin (Hb) level of >115. The data was analysed to see how many patients in ORU were transfused above this level. This level being a clinical indicator of possible inappropriate transfusion. From a group of 114 patients, which includes 70 hip and 44 knee replacements, 44 were transfused a total of 157 units of packed cells. 39% of patients were transfused an average of 3.6 units. Of the transfused group 39% completed their transfusions with a Hb >115 which may be demonstrating over transfusing. From this base line data the RHH Blood Matters Team developed strategies.

- Taking a Haemoglobin level later in the day to alleviate the dilution affect in the post operative period.
- The newly appointed Transfusion Nurse started and continues
- Daily contact with medical staff in the wards,
- Auditing the decision making process
- Feeding back information.
- Academic detailing of individuals and groups

The base line data was then compared to data gathered for Jan-June 2003 after a time of intensive application of the strategies to see if this has resulted in altered clinical decision making. From a group of 154 patients, which includes 115 hip and 39 knee replacements, 48 were transfused a total of 144 units of packed cells. 31% of patients were transfused an average of 3.0. Of the transfused group 12.5% completed their transfusions with a Hb >115. From this data we have concluded that the education on the NHMRC guidelines has indeed altered the clinical practices of the medical staff in the ORU. The lowering of the post transfusion Hb and the reduction in the number of units transfused has reflected this. An estimation of the units saved in ORU is 140 units for 2003, which equates to a dollar factor of AU $33,120 if the total cost of each unit to the state is AU $230. The ORU uses approximately 10% of the total blood transfused at RHH so the potential cost savings in dollars and the conservation of the blood supply will be many fold more when the same strategies are extended to the rest of our hospital.

258

They Do What with It? Tales from the Other Side of the Counter and why you might need a Transfusion Nurse Consultant

Quested B[1], Hunt R[2], Roffey T[3], Verrall T[4], Davis K[1], Hetzel P[5], Thorp D[5], Robinson K[5]

[1]Royal Adelaide Hospital-Adelaide, [2]Flinders Medical Centre -Adelaide, [3]Queen Elizabeth Hospital -Adelaide, [4]Women's and Children's Hospital -Adelaide, [5]Australian Red Cross Blood Service-South Australia

BloodSafe is a state wide collaborative project sponsored by the South Australian Hospital Safety and Quality Council of the Department of Human Services and Australian Red Cross Blood Service-SA. The aims of the project are to improve blood transfusion safety and efficiency. This paper details some of the anecdotal evidence to support the need for the ongoing role for a transfusion nurse and an educational program in transfusion practices. As a part of the BloodSafe project nurses collected anecdotal evidence of incidents within their institutions. At least one serious 'near miss incident' was noted each week. The anecdotes were grouped by category which included: Potential for wrong blood to the wrong patient; Potential for inappropriate transfusion; Consent process; Autologous collection/transfusion; Patient Comments; Staff comments; Handling & administration; and 'Other'. These anecdotes relate to 'real life' situations in which blood products are used (and misused) and to practices that seriously affect

the overall safety of transfusion. They highlight 'systems' that made mistakes more likely; a lack of awareness of correct policy, procedures and transfusion knowledge by various staff groups; and suboptimal blood product handling. In recent times the viral risks of blood have diminished considerably. Major improvements in blood transfusion safety at the clinical interface from will result from ensuring safe transfusion practices. While these anecdotes relate to institutions involved in the BloodSafe project we believe they are not unique instances and similar events probably occur in other institutions. The BloodSafe transfusion nurses provide an important mechanism by which hospital staff and laboratory staff can communicate their concerns about transfusion practice. Communication about actual and potential problem areas has increased as staff members see improvements in practice and, words became actions. Support of all hospital staff involved in the transfusion process needs to occur to ensure that blood transfusion is safe from 'vein to vein' and not from 'vein to the transfusion laboratory door'.

259

Implementation of A Statewide, Structured Transfusion Nurse Role: Integrating the role into a hospital environment and the transfusion team to assist in delivering sustainable, long-term improvements in transfusion

McKenna R[1], Botting K[2]
[1] Blood Matters, Royal Melbourne Hospital, Melbourne, [2]Blood Matters, Australian Red Cross Blood Service, Victoria

Background: Published Australian studies have indicated that 20 – 50% of transfusion events involving fresh blood products are inappropriate and that recommended transfusion practices are not followed. In 2002, the Victorian Department of Human Services funded a Pilot Consortium - the Australian Red Cross Blood Service-Vic, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre - to develop sustainable and transferable improvements in transfusion practice for use in 2003 by the Blood Matters Breakthrough Collaborative hospitals that encompassed 15 public hospitals across Victoria. As many disciplines are involved in transfusion practice, a key to delivering sustainable, long-term changes was considered to be the development of a specific nursing role with appropriate qualifications in transfusion. We present how that role has evolved to become an integral member of the transfusion team. Method: The Pilot Transfusion Nurses underwent a certificate level education program with lectures in Transfusion Medicine, Project Management, Auditing, and Academic Detailing. As the project developed, the nurses' experiences informed the development of the Graduate Certificate in Transfusion Practice for delivery beyond the collaborative. Using 'Breakthrough' methodology developed by the Institute of Healthcare Improvement in America, the Pilot used data from existing published studies to develop practical concepts for local practice improvement in the areas:

1. Aligning clinician decision-making about transfusion with NHMRC/ASBT guideline recommendations
2. Enhancing patient understanding of the risks and benefits of transfusion
3. Improving the capture of error and adverse events in transfusion practice
4. Improving blood product and patient/sample identification
5. Improving handling and storage of blood products
6. Improving the protocols and procedures for administration of blood products.

The Transfusion Nurses were integral in the development and trial of the concepts.

260

Baxter Amicus® Crescendo Separator utilising the New Version 2.5 Software: collection of double dose apheresis platelets suspended in t-sol whilst maximising concurrent plasma volumes

Dennington P.M[1], Johnston S[1], McEwen A[1], Stewart IM[1], Regan J[1], Walker H[1], Walker S[1], Ireland K[2], Moore G[2]
[1]Australian Red Cross Blood Service New South Wales, Sydney, [2]Baxter Healthcare Pty Ltd, Sydney.

Background: Current apheresis technologies provides apheresis platelets suspended in plasma. The Amicus® Crescendo Separator allows collection of apheresis platelets with partial replacement of plasma with a platelet additive solution (*T-sol*) which can be expected to reduce the incidence of febrile platelet transfusion reactions. Additional plasma for fractionation can also be harvested from the same donation. The primary objective of this study was to perform an Installation Qualification / Operational Qualification (IQ/OQ) on the Amicus® Crescendo Separator with the new version 2.5 software, demonstrating that routine use of this fully automated apheresis system provides blood components that meet the ARCBS - NSW quality requirements. The secondary objective was to maximise the number of double plateletphereses (6.0×10^{11} platelets/pack) collected whilst maximising concurrent plasma volumes. Platelet concentrates were resuspended with saline and stored in Plasma and *T-Sol*. Methods: Donor selection criteria were previous plasmapheresis donors with a platelet pre-count above 200×10^9 platelets / L (note: no minimum donor pre-count was specified to increase ratio of double platelet doses). Donor's post-count was required to be above 100×10^9 platelets / L at the end of Plateletpheresis and the maximum estimated collection time was not to exceed 100 minutes. Amicus® Crescendo estimated that 14 donors were suitable for double platelet collections and 6 donors were suitable for single platelet collections. All 20 units were suspended in *T-Sol*. All donors were targeted for high volume concurrent plasma collections. The final Platelet product was analysed for platelet count, size (MPV), WBCs, pH, swirl and microbial contamination. Plasma products were analysed for WBC, RBC, platelet content, plasma Hb, and Factor VIII levels. Results: Thirteen of the fourteen donors that the Amicus® Crescendo Separator predicted would be capable of providing a double platelet product met the target. The average yield was $6.25 \pm 0.64 \times 10^{11}$ in only 81 ± 10 minutes. Venous access issues caused the fourteenth donor to donate a single product. All six donors that the Amicus® Crescendo Separator predicted would donate a single platelet product met this yield with an average count of $3.30 \pm 0.41 \times 10^{11}$ in 60 ± 8 minutes. The average volume of the plasma product was 489 ± 25 mL when collected with a double platelet product and 528 ± 44 mL when collected with a single platelet product. Other quality parameters were met after minor changes to machine settings. Conclusion: The use of the Amicus® Crescendo Separator utilising the new Version 2.5 Software has demonstrated a high collection efficiency enabling high split rates of above 70%. The addition of *T-Sol* platelet additive solution has maximised concurrent plasma harvest with average yields of 500 mL per donation. These two enhancements will enable blood banks to maximise the number of therapeutic platelet units collected and increase plasma volumes from a shrinking donor base.

Results: Hospital wide policy changes in some of the above mentioned areas have occurred

- Blood Matters Breakthrough collaborative commenced on schedule with 15 Victorian Hospitals and 1 Tasmanian hospital participating.

- The Collaborative hospitals commenced their project with the aid of practical change packages developed by the Pilot Consortium consisting of concepts, processes, plans and tools.
- 16 transfusion nurses from participating hospitals commenced a Graduate Certificate in Transfusion developed and implemented by the Blood Matters Education Project and the University of Melbourne.

Conclusion: This structured, statewide implementation of the project Transfusion Nurse has been successful at instigating improvements in transfusion practice. The next phase of the pilot project will be to test the sustainable integration of these improvements into hospital practice.

261

Evaluation of a New Donor Arm Disinfectant

Wong PY, Colville V, White V, Walker H, Morris R, Candy S
Australian Red Cross Blood Service, Melbourne, Victoria, Australia.

Objective: To validate a new antiseptic as a standard donor arm disinfectant. Design and setting: A prospective study of bacteria present on blood donors' arms before and after disinfection with a disposable applicator containing 1% chlorhexidine gluconate with 75% ethanol (Persist Plus™, supplier Becton Dickinson). Staff and donor feedback on the applicator was obtained using a questionnaire. Subjects and methods: Permission was asked randomly from 200 donors each from three types of blood collection venues – fixed, mobile, and regional (rural) to be enrolled in the study. The antecubital fossa of the non-donating arm was tested by a direct swabbing and plating technique pre- and post-disinfection with the antiseptic Persist Plus™. Normal venesection and blood collection then occurred from the opposite arm. Data entry and analysis of the questionnaires was performed using Epi-Info 2002. Results: Pre-disinfection, 56 % of 616 donor arms had colony counts of <5 cfu/plate and 64% had counts of <10 cfu/plate. After disinfection with Persist Plus™, 99% of donor arms had counts of <5 cfu/plate and 99.5% had counts of <10 cfu/plate. There was no significant difference in the bacterial counts from donors in different blood collection venues. The mean colony count for all donors post-disinfection was 0.39. Overall, the percentage reduction in bacterial counts of 99.0 was obtained. These results compared favourably with studies reported from the National Blood Service, UK, using other common disinfectants such as Medi-Flex. Most donors found the smell or green colour of the disinfectant to be acceptable (99% and 91% respectively), and 16 donors (3%) reported transient skin irritation. The majority of donors (80%) either preferred or did not object to the new disinfectant replacing the current preparation. Discussion and conclusion: The Australian Red Cross Blood Service had been searching for a standard national disinfectant to replace the several preparations currently in use for donor arm preparation prior to venesection. The disinfectant Persist Plus™ was found to be suitable both from the bacteriological and end-user acceptance points of view.

262

The Provision of Non-Refrigerated Whole Blood for Bali Bomb Victims: A Donation to Transfusion Perspective

Finch S[1], Carnley B[1], Cobain T[2], Dunmow R[2], Wood F[1], Goodwin-Walters A[1], Herrmann R[1]
[1]Royal Perth Hospital, [2]Australian Red Cross Blood Transfusion Service, Perth.

As a result of the Bali bomb explosions in October 2002, Royal Perth Hospital (RPH) received 23 patients who required treatment for burns. Among these were 6 patients with major burns ranging from 28% to 85% of their total body surface area. These patients required extensive surgical procedures in relation to their burns injuries. Surgery was scheduled for the patients with major burns, along with a number of patients with minor burns, over five consecutive days. Meetings were held involving hospital staff and an Australian Red Cross Blood Service (ARCBS) representative, to determine a strategy for the provision of blood products. In relation to the surgical procedures- particularly burns debridement, it was believed there could be a potentially high demand for ARCBS products. Traditionally, separate component products would have been requested; however based on prior experience using in-house untested, non-refrigerated whole blood, the decision was taken that the use of tested, non-refrigerated, whole blood would result in the most efficient and effective use of blood product. Dealing with this new product in large quantities led to a number of challenges for both the RPH transfusion medicine staff and the ARCBS. The ARCBS, although having many potential donors due to the media coverage of the explosions, needed to supply blood for patients with rarer blood types. Surgical procedures requiring non-refrigerated whole blood were scheduled to take place over a weekend, when routine ARCBS processing of donors and products did not normally occur. The timing of donor appointments and testing of the donors had to be considered in relation to the 24 hour time limit imposed for the storage of non-refrigerated whole blood. From the transfusion medicine laboratory viewpoint, it was unknown how effective the whole blood would be as a stand-alone product, so initially extra quantities of blood components were placed on stand-by. New procedures had to come into place to ensure the correct handling of the whole blood by theatre staff, and various issues relating to the use and storage of the product had to be dealt with as problems arose. In conclusion, the use of non-refrigerated whole blood raised a number of unique issues with implications involving laboratory management. Lessons learnt from this experience will be applied to future disaster management plans.

263

The Rare Donor Programme of the International Society of Blood Transfusion (ISBT)

Woodfield G
Dept of Molecular Medicine & Pathology, University of Auckland

The ISBT has had a Rare Blood donor programme in operation since 1965. It is managed from the International Blood Group Reference Laboratory (IGBRL) in Bristol, England. From here access can be obtained to the International Donor Panel (IDP). Supporting the programme is the ISBT Working party (ISBTWP) on Rare blood donors which commenced in 1985. The ISBTWP is active in education on many aspects of rare blood and develops operational guidelines for Blood Services. New guidelines are soon to be published. Seminars have been held at National and International congresses with the result that there is now wider involvement in the programme. The IDP has over 4000 donors on its roll but constantly needs additions to replace donors who retire and also to supply blood specificities that are in short supply. A survey in 1999 revealed that over 2000 units of rare blood were transported yearly, either nationally or

internationally, to meet the needs of patients with rare or complex antibodies. Most requests can be met but there is a shortage of phenotyped donors of some blood types. This important programme deserves the full support of Blood Services. In those countries where there are a well developed facilities, it is very helpful if a rare donor screening programme is in operation. NZ and Australia have made a significant contribution in the past by supplying Gerbich and Kidd negative rare blood as well as some other types. The need for rare blood is a relatively rare event but when it occurs it is very helpful if all are aware of the steps that need to be taken to assure rapid and safe delivery. NZ and Australia are urged to attach a higher priority to this area of transfusion medicine.

264

Non Refrigerated Fully Tested Whole Blood & Major Burns: A Prospective Transfusion Audit of Clinical Efficacy

Carnley BP[1], Finch S[1], Cobain TJ[2], Boyd S[2], Eddy P[2], Dunmow R[2], Lown J[1], Goodwin – Walters A[1], Wood F[1], Herrmann R[1]
[1]Royal Perth Hospital, Perth, [2]Australian Red Cross Blood Transfusion Service, Perth

Aim: To document the use of Non-Refrigerated fully tested Whole Blood, in the early surgical debridement of a cohort of patients with major Burns and Blast injuries, in terms of clinical efficacy.
Method: A prospective audit of blood product use during initial surgical debridement undertaken at Royal Perth Hospital, of patients with greater than 25% total body surface area (TBSA) burns sustained in the Bali bomb explosions in October 2002, was undertaken. Blood product use during the intra-operative period was recorded. Haemoglobin, Platelet count, International Normalised ratio (INR), Activated partial thromboplastin time (aPTT), fibrinogen and PFA100 platelet function data were recorded as they were requested by the clinical staff at the bed side. Data was collected during the initial debridement surgery, and for the immediate preoperative and postoperative periods. Results: Six patients with between 28 and 85% TBSA burns underwent initial debridement surgery (300 to 615 minutes duration). During the operations between 7 and 17 units and a total of 67 units of fully tested fresh whole blood were transfused; no other blood products or recombinant haemostatic agents were required. The haemoglobin range for the preoperative, intraoperative and postoperative periods was 77 – 120, 77 – 132 and 87 – 129 g/L respectively. Five patients ended their procedures with higher haemoglobins than at the commencement. Four patients maintained a platelet count of greater than 100 x 10^9 / L and one maintained a platelet count between 53 and 72 x 10^9/ L throughout the perioperative period. One patient was thrombocytopaenic preoperatively (22 x 10^9/L) and maintained an improving platelet count during the intraoperative period to have a postoperative count of 85 x 10^9 / L. PFA 100 closing times during the intra and postoperative periods remained below the upper limit of the normal range. All patients maintained an INR between 1.0 and 1.4 and an aPTT of between 29.4 sec to 42 seconds during the intra and postoperative periods. One patient had an aPTT above the normal range postoperatively. Whilst there was a statistically significant ($p=0.05$) fall in fibrinogen levels across the perioperative period, all patients maintained levels of fibrinogen that were greater than the lower end of the normal range. Two patients died from overwhelming sepsis at day 4 (85% TBSA) and day 56 (83% TBSA) post initial debridement surgery. Conclusions: The use of non refrigerated fully tested whole blood in the setting of major burn debridement was associated with minimal coagulopathy and may reduce recipient exposure to multiple donors.

265

Making Life Easier: fresh frozen plasma with a 5-day post-thaw expiry

Winzar SA, Wood EM, Constantin G
Australian Red Cross Blood Service, Victoria

Aim: Expiry of Fresh Frozen Plasma (FFP) and Cryoprecipitate-Depleted Plasma (CDP) has traditionally been 24 hours (h) post-thawing. The aim of this study was to investigate coagulation factor levels in plasma during extended refrigerated storage, hoping to allow greater clinical flexibility and reduce product wastage.
Method: Components [30 FFP (10 group A, 1 AB, 3 B, 16 O) and 30 CDP], were prepared by routine processing methods. FFPs were split into 2 before freezing: groups I and II. These were thawed, (day [d] 0), in a 37^{o}C waterbath. Group I was sampled immediately, group II left at room temperature (RT) for 4h. After sampling, all were stored at 2-6^{o}C. Group I FFP was sampled on d 1,2,3 and 4 (i.e. days *after* thawing); Group II on d2 and d4. All were tested for levels of factors (F) V, VIII and fibrinogen on d0 and d4; also vWF antigen tested in CDP (d0) and FFP II (d0 and d4). Thawed FFPs (n=107), left at RT for 4–6h, then stored until d4 at 2-6^{o}C, were sent for microbial testing. Results: FV, fibrinogen and vWF levels in FFP showed no significant decrease over 5d. FVIII decreased initially then stabilised. Mean levels were 1.08±0.33 IU/mL (d0), 0.72±0.2 (d1) and 0.56±0.15 (d4). Mean FV was 0.89±0.14 IU/mL (d0) and 0.75±0.13 IU/mL (d4). Mean fibrinogen was 279±51mg/dL (d0) and 275±50 (d4). vWF levels did not change [98±32 % (d0) vs 94±27% (d4)]. There was no significant difference between groups I and II. In CDP, FVIII was 0.12±0.03 IU/mL (d0) and 0.10±0.13 IU/mL (d4). VWF was 10.8±3.4% (d0) and not assayed on d4. Fibrinogen and FV levels in CDP remained reasonably constant over 5d. All 107 units tested negative for microbial contamination. Conclusion: Mean labile coagulation factor levels remained adequate for haemostasis, (ref. AABB Technical Manual 2002), during extended refrigerated storage including a period at RT for up to 4h. ARCBS now states that expiry of thawed FFP and CDP can be extended to 5 d from thawing, if refrigerated at 2-6^{o}C and relabelled as 'Thawed Plasma' (*Circular of Information 2003*). Note: these units should not to be used to treat FVIII deficiency. Routine extended expiry of thawed plasma may allow improved laboratory and clinical flexibility and reduced wastage of precious plasma supplies.

267

Massive Haemorrhage: A Transfusion Laboratory Perspective

Savoia H
Women's & Children's Health, Division of Laboratory Services, Parkville, Australia

Obstetric haemorrhage is a significant cause of maternal mortality. At term, blood flows through the placenta at 70ml/min so blood loss is likely to be rapid. Obstetric haemorrhage is often unexpected, and can be massive, life threatening for mother and baby, and can be accompanied by disseminated intravascular coagulation. This talk will outline an approach to management of this problem which is based on routine use of a management protocol, and recognises the different skills brought by members of the management team who work together to maximise patient outcome. The key players in the team are the obstetrician, anaesthetist, haematologist, midwifery staff, theatre nurse and laboratory scientist. In some circumstances the gynaecological oncologist or interventional radiologist is involved. Each player has a unique role and brings skills which are respected by other team members. Successful outcome depends on:

- Routine use of a management protocol which all staff are familiar with
- Clear communication between clinical and laboratory areas

- An agreed procedure for the rapid provision of blood in an emergency
- Training and competence of staff who transport laboratory samples and blood products
- Effective haematology and transfusion laboratory support.

269

rFVIIa for Massive Haemorrhage: a clinical usage audit

Street A[1] and Hruska J[2]
[1]Haematology Unit, The Alfred, Melbourne, Australia
[2]Novo Nordisk, Baulkham Hills, Australia

Uncontrollable haemorrhage is an acute emergency that is associated with significant morbidity and mortality. It is important that physicians regularly audit clinical outcomes and transfusion requirements in such patients, so that best practice continues to be refined and implemented as our knowledge of clotting mechanisms and management options are also refined. Although developed for treatment of bleeding in patients with haemophilia A and B with inhibitors, recombinant factor VIIa (rFVIIa) has been used globally for the treatment of acute bleeding in a number of situations outside this indication. This experience is being captured on *Haemostasis.com*, an international, internet-based registry established with an educational grant from Novo Nordisk. In the absence of data on safety and efficacy from randomized trials, we rely upon registry submissions. This presentation will review current clinical practice for the management of uncontrollable bleeding from two perspectives: a global perspective from cases submitted to *Haemostasis.com* and an Australian and New Zealand perspective from cases submitted to the same database.

1. International registry

The *Haemostasis.com* registry has been active since June 2001 and to date has accumulated more than 800 cases of emergency bleeding treated with rFVIIa. From the total registry, patients with uncontrollable haemorrhage have been identified by using an automatic search function to select patients who received blood products (packed cells and/or fresh frozen plasma) before rFVIIa administration. This subgroup has been analysed in detail, and the following findings will be presented:

- Countries submitting records of uncontrollable bleeds to the database
- Aetiology of uncontrollable bleeds
- Severity of the haemorrhage
- Audit of the use of rFVIIa (doses used, effect of rFVIIa on haemorrhage, amount of blood products required before and after rFVIIa administration, adverse events and outcomes).

2. Australian and New Zealand experience

Since 1998, rFVIIa has been used in approximately 170 non-haemophiliac patients with uncontrollable haemorrhage in Australia and New Zealand, 81 of these during 2003. To date, 21 such cases have been entered into the *Haemostasis.com* database, mainly associated with trauma or major surgery. An overview of these 21 cases will be presented, focusing on the blood products/replacement fluids administered, active treatments given and the outcomes.

Note: The *haemostasis.com* registry is managed by an independent agency on an unrestricted grant from Novo Nordisk.