Medications, Intravenous Fluids and Blood for Transfusion

The complications associated with the addition of medications and intravenous fluids into units or the mixing in the infusion lines of blood components and blood products is an avoidable hazard in the practice of blood transfusion. Blood components are biologic and in some cases living tissues. Once outside the body blood is an extremely fragile commodity. Blood components are quickly damaged or denatured by chemical or physical insult. It is for this reason that the storage, handling and transfusion of blood components are subject to such rigorous controls and monitoring. Blood outside the body does not have the same metabolic homeostatic protection as blood flowing in arteries or veins.

Only isotonic (0.9%) saline or 5% human albumin should be used to dilute blood components, because other intravenous solutions may damage the red blood cell and cause haemolysis (dextrose solutions) or damage platelets (amphotericin), or initiate coagulation in the infusion set (calcium containing solutions). In addition many drugs will cause haemolysis of the red cells, or damage to platelets or plasma proteins if they are injected into the blood transfusion set line. A break in the integrity of the blood container or infusion line also increases the chance of bacterial contamination of the component and product that is being transfused.

Only those drugs, which have been delivered by a validated procedure and shown not to cause damage and cause no harmful effect to a patient in the clinical setting in which they are used, may be permitted to be mixed ex vivo with blood components and blood products. There are so few studies that meet this requirement and the frequency of adverse reactions is so high that the precautionary principle that no medications or solutions (other than isotonic saline) should be added to blood transfusion set lines is invoked.

The possible exception to this guidance is the use of intravenous continuous narcotic infusions and patient controlled analgesia. Studies at Wellington Hospital1,2 ICU have demonstrated that no adverse reactions occur when such infusions are set up with 0.9% saline, as opposed to 5% dextrose. This approach should only be utilised however when it has been formally approved in established hospital policy guidelines.

References:

Transfusion Nurse Specialists

NZBS is committed to support clinicians in providing high quality products and services for patients across New Zealand. In the larger DHBs NZBS is also directly responsible for provision of hospital transfusion services and this involves management of the hospital blood bank and provision of specialist clinical support.

As part of this commitment NZBS has recently appointed Transfusion Nurse Specialists in Dunedin (Suzi Reidworth), Christchurch (Angela Wright), Wellington (Catherine Hammond) and Auckland (Rachel Donegan) to join the NZBS nurse in Waikato (Christopher Corkery). The primary role of these nurses is to provide excellence in the practice of transfusion medicine by the provision of specialist knowledge, quality activities and staff education. Key priorities for the role involve clinical audit of blood component and product use and education of the DHB staff in the appropriate use of these products. Audit initiatives will be developed in conjunction with the DHB staff and will focus on improving the overall utilisation of blood products.

Some of the critical elements to the success of these appointments are administrative, human resource and professional support for an activity that requires substantial specialist knowledge as well as highly developed professional and interpersonal skills to operate effectively in complex and varied environments.

Other critical elements are the NZBS/DHB partnership, the joint commitment to meet best practice performance as well as ongoing dialogue to agree specific projects and priorities while working closely with and through the respective Transfusion Committees.

Transfusion Medicine Handbook 2003

The Transfusion Medicine Handbook has now been published and is designed to assist hospital staff and other health professionals in modern Transfusion Medicine Practice. The book is directed to all staff who are responsible for prescribing, supplying and administering blood products. They include:

- Medical staff who assess the patient, prescribe and order the product to be transfused.
- Laboratory and pharmacy staff who receive the order and prepare the product, to ensure that the product is compatible for transfusion to the patient.
- Orderlies and transport personnel who deliver the product to a hospital ward or clinic where the patient is being treated.
- Nurses and other clinical staff who check that the product is for the identified patient before it is administered and who observe the patient during and after the transfusion.
- Telephone operators who may have to make vital contacts in an emergency.
- Medical and nursing students.
Correctly used, blood and blood products can save lives and provide clinical benefit to many patients. However, the effectiveness of much of blood transfusion practice today has not been rigorously proved by clinical trials. It is therefore not possible to give a complete evidence based guideline for practice. Where good evidence is not available, the contents reflect our best effort to give a balanced view of current opinion about clinical practice in transfusion for patients in New Zealand.

In addition to information about the blood products and services made available by the NZBS, it provides a framework for the clinical indications for the use of, the procedures for administration and the adverse reactions to the use of these products in patients. Most of the problems associated with transfusion that cause delays and may put the patient at risk are caused by:

- Poor communication.
- Failure to follow documented procedures.
- Inadequately trained staff.

The most frequently occurring problems are:

- Prescribing blood products that are not required by the patient or are not the most suitable treatment for the patient's clinical condition.
- Incomplete or inaccurate completion of request forms or sample tube labels.
- Delays caused by a failure to communicate accurately when and where blood is needed.
- Transfusion of blood products that were intended to be given to someone else.
- Failures to recognise and react effectively to evidence of adverse reactions that occur during transfusion.

This handbook is freely available through the Transfusion Nurse Specialists or from Irene Wai-Poi, New Zealand Blood Service National Office, 71 Great South Road, Epsom. Telephone 09 523 5763, email irene.wai-poi@nzblood.co.nz

**IgA Deficiency and Transfusion**

Deficiency of immunoglobulin A (IgA) is the commonest primary immunodeficiency disease affecting humans. The disorder affects approximately 1 in 700 people of Caucasian, African or Arab ethnicity but is far less common in people of Asian ethnicity. IgA is one of five classes of antibody present in the blood (IgG, IgA, IgM, IgD, IgE) and is second in concentration after IgG. It is the main immunoglobulin present in secretions and it is likely that it plays an important role in protecting mucosal surfaces from infection.

IgA deficiency may be total or partial. There is no universal consensus on the definition of IgA deficiency, however total IgA deficiency represents the smaller subgroup. Most studies have defined total IgA deficiency as IgA <0.05 g/L however some testing centres employing more sensitive detection techniques have recently lowered the cut off point to <0.0016 g/L. Partial IgA deficiency is considerably more common and describes detectable but reduced IgA.

Many early reports indicated that two out of three individuals with IgA deficiency are healthy. However, this data was largely based on assessments of healthy blood donors in whom IgA deficiency had been detected incidentally and involved no follow-up. Twenty year follow-up of initially healthy blood donors with IgA deficiency has been instrumental in shedding more light on this disorder. This follow-up has revealed that as many as 80% of individuals with total IgA deficiency (<0.05 g/L) suffer from an increased susceptibility to sinopulmonary infection, autoimmune disease (especially coeliac disease) and gut or thyroid malignancies. Despite this morbidity, no evidence of a reduction in lifespan has been found in those IgA deficient individuals first identified as healthy blood donors.

One of the most important aspects of IgA deficiency for patients and clinicians is the risk of serious or life threatening reactions to transfused blood or blood products that contain IgA. These reactions are frequently anaphylactic in nature and are often associated with anti-IgA antibodies. Notably, serious reactions in the absence of detected anti-IgA antibody have also been reported.

Anti-IgA antibodies are usually of IgG class but can be IgM or IgE. The alloantibodies are usually class specific (anti-α-chain) and are found almost exclusively in patients with total IgA deficiency. Conflicting reports have also described anti-IgA antibodies in normal sera with frequencies ranging from 2-59%. These discrepancies probably result from methodological differences and have impaired our ability to determine the clinical significance of detecting anti-IgA antibodies.

Alloantibodies directed against IgA develop in 20-40% of individuals with selective total IgA deficiency, in approximately 30% of those with common variable immunodeficiency (deficiency of IgG and IgA +/- IgM) and in greater than 60% of patients with combined IgA and IgG subclass deficiency. Anti-IgA is thought to develop following exposure to maternal IgA in breast milk or during intrauterine life, or following exposure to IgA-containing blood products.

A look back at the recipients of blood products donated by 13 individuals with total IgA deficiency and high titre anti-IgA (identified by screening 73,569 donors) found no cases of anaphylactic reaction following passive administration of anti-IgA to normal recipients.

The importance of anti-IgA antibodies in causing and predicting adverse reactions in IgA-deficient patients receiving IgA containing blood products remains controversial. The method of detection and class of anti-IgA may be important variables. Numerous studies suggest that high-titre, class-specific IgG anti-IgA is often but not always associated with adverse reactions.

Severe anaphylactic reactions have been associated with high-titre IgE anti-IgA in at least one study. However, detection of anti-IgA antibodies in a recipient is neither sufficient nor essential to cause adverse reactions and testing outside of specialised centres is a poor predictor.
cryopreserved or an IgA-deficient donor can be autologous platelets may be pre-donated and such a way that virtually no plasma remains. Alternatively donation. Allogeneic platelets must be prepared in or can be collected through autologous pre-washed (or frozen-thawed-washed) to remove IgA, or treated to remove IgA. Red cells are typically rare IgA-deficient donors (usually with total IgA high-titre anti-IgA, require IgA-deficient products. The product may be either autologous, derived from IgA-deficient donors (usually with total IgA deficiency and identified through a rare donor program), or treated to remove IgA. Red cells are typically washed (or frozen-thawed-washed) to remove IgA, or can be collected through autologous pre-donation. Allogeneic platelets must be prepared in such a way that virtually no plasma remains. Alternately autologous platelets may be pre-donated and cryopreserved or an IgA-deficient donor can be sought. Plasma products (e.g. FFP or cryoprecipitate) must be obtained by autologous pre-donation or from an IgA-deficient donor.

Weeky immunoglobulin (IVlg) is a special case. Because of the risk of IgA sensitisation IVlg therapy is normally avoided in patients with selective IgA deficiency. However IVlg therapy may be warranted for patients lacking both IgG and IgA who are susceptible to recurrent life-threatening infections.

The IgA content of IVlg depends on the manufacturing process and may vary between brands from <10 mg/L to >500 mg/L. Patients that react to preparations containing higher levels of IgA may not react to an alternative brand that contains only trace amounts of IgA. Several publications suggest that delivery of immunoglobulins via the subcutaneous route using intramuscular (IM) preparations is safe even when these products still contain some IgA. The IM route however, like the intravenous route, is known to provoke anaphylactic reactions. Provision of IgA-deficient IVlg is possible by means of IgA-immunodepletion or IVlg chromatographic-puriﬁcation. Alternatively plasma derived from IgA-deficient donors may be used as a substitute for IVlg when even trace amounts of IgA remain problematic.

Although anaphylaxis related to IgA deficiency poses a difficult but fortunately rare problem for transfusion services world-wide, modern transfusion technology and planning has allowed individuals with this disorder to access a full range of surgical or medical interventions that otherwise may be virtually impossible to offer.

West Nile Virus

West Nile Virus was first isolated in 1937 from an infected person in the West Nile district of Uganda. Prior to 1999 the virus was found only in the Eastern hemisphere with wide distribution in Africa, Asia, the middle East and Europe. In 1999 the first case of the disease was identiﬁed in the United States of America. During 2002 there was a signiﬁcant increase in the number of cases occurring in the US. West Nile Virus is an anthropod-borne RNA lipid envelope virus of the genus Flavivirus. Included in this group are Murray Valley encephalitis, Japanese encephalitis, yellow fever and dengue. It is primarily transmitted in birds through mosquito bites while humans are incidental hosts. The incubation period is thought to range from 2-14 days following infection by mosquito bite and most people infected by WNV do not develop any illness. The possibility of transmission by blood transfusions or organ transplants was ﬁrst raised in the US after four recipients of organs from one woman contracted West Nile Virus infection and a woman contracted the disease after receiving transfusion from three infected donors.

During 2002 the United States and Canada experienced a severe epidemic of WNV. Transmission by transfusion of blood components was conﬁrmed in a number of patients, including fatalities. Interestingly no cases of transmission occurred following transfusion of fractionated blood products. This demonstrates the efﬁcacy of the speciﬁc viral inactivation steps used in their manufacture.

More than 400 cases of West Nile Virus Infection (with 16 fatalities) were reported to the Centers for Disease Control and Prevention by 22 states of the USA during the week ending September 3 2003. These cases comprised more than 20% of the total 1,856 human WNV cases reported since the beginning of this year’s epidemic, suggesting that the epidemic is on the up-slope if not at the actual peak.

So far this year, the epidemic has been very focal, with ﬁve states accounting for about two thirds of the cases; Colorado, Nebraska, South Dakota, Wyoming and Texas. In contrast, the states with the largest number of cases last year – Louisiana, Mississippi, Michigan, Illinois and Ohio have reported relatively few cases so far. Only six states have reported no WNV activity in humans, birds, animals or mosquitoes. CDC also reported a total of 157 presumptive WNV viremic blood donors. Of these donors, 12 subsequently had WNV fever and none subsequently had WNV meningoencephalitis. United States and Canadian Blood Services have implemented nucleic acid testing of all donations to reduce the risk of transmission.

WNV infection has not been reported in New Zealand and the vector mosquito is not present in this country. The possibility that individuals who have recently visited the United States and have been bitten by mosquitoes which might carry the infection cannot be excluded. Should such an individual donate blood then this could be transmitted by transfusion.

As a precautionary measure NZBS introduced a new donor standard on the 5th May 2003 aimed at reducing
the risk of transfusion associated West Nile Virus in New Zealand. This standard requires that the donations from donors who have returned from the USA and Canada within the six weeks preceding donation are used for plasma fractions only during this six week period. Fractionated plasma products currently available include dedicated viral inactivation steps during the manufacture which are highly effective in removing enveloped viruses such as West Nile Virus. A similar standard was introduced in Australia on the 1st of July 2003 and similar measures have been adopted in Europe.

**Joint DHBNZ/ DHB and NZBS Workshop on Haemophilia Treatment Issues**

A workshop on haemophilia issues that included DHBNZ/ DHB and NZBS as participants took place on the 25th June 2003. The workshop concluded that the current arrangements for funding of Haemophilia care within New Zealand are a barrier to the development of a nationally consistent service. The funding issue will need to be addressed before other current issues can be properly assessed.

Responsibility for defining alternative arrangements to support a nationally consistent and equitable service lies with the DHBs and this will most effectively be achieved through DHBNZ. The status quo position should be maintained until new arrangements have been defined and agreed, including the current mix of products used for management of Haemophilia at both local and national levels. A project will be established to take responsibility for the development of a proposal to DHBNZ for the national co-ordination and management of Haemophilia Services. The proposal will incorporate:

- Access criteria, exclusions and limitations for a nationally funded mechanism for service funding and delivery. This will include an analysis of cost-benefit.
- The definition of a clinical board that will take responsibility for development of updated clinical guidelines and a proposal for the development of a clinical registry.
- An assessment of the role of Bioquant in New Zealand which will be undertaken once the above system has been defined and implemented. A decision by the end of February 2004 will be required to enable any consequences to be incorporated into the 2004/05 planning cycle.

NZBS will construct a model to assess the optimal mix of plasma derived versus recombinant Factor VIII. This model will in particular review the impact of capping plasma derived Factor VIII production to the level of demand for Intragam P.

- The model will be used to define a number of possible options for consideration at a national level through DHBNZ.
- The model will also address the financial and supply issues associated with a possible switch to Bioquant from AHF, as well as the financial and supply issues of an unmanaged switch to recombinant from AHF.

- This process will be completed by October 31st 2003.
- NZBS will define and implement information systems to support proactive demand management. This will incorporate data on both plasma and recombinant product use.
- NZBS will define data requirements for recombinant use and supply this information to ADHB and CDHB.
- NZBS will define and construct a system to support a nationally consistent and equitable service. This will be reviewed on a regular basis.
- Recombinant Factor VIII will be the primary contingency supply in the event of severe shortage of AHF.
- NZBS will maintain contact with Australian authorities regarding AHF but will not import Australian product unless significant supply problems develop.
- NZBS will monitor AHF and recombinant stocks on a regular basis and communicate this information to the Haemophilia Treatment Centres.
- NZBS will manage supply by split dispensing and similar approaches.
- NZBS will promote responsible clinical use during periods of anticipated shortage.

**Adverse Reaction Reporting**

Most patients receiving blood components or blood products do not experience adverse effects. Others may have mild to severe effects, immediately after the commencement of the transfusion or up to 48 hours later. The reporting of adverse reactions provides data that is collected, collated and monitored both at the request of Medsafe and for the purposes of New Zealand Blood Service, to provide an early warning system of adverse reactions. It is intended that the monitoring programme will result in timely advice from NZBS to the manufacturer of fractionated products and where appropriate to the prescribers of the product.

Reactions may arise from individual blood products and particular concern exists for detection of reactions to new or modified products. Reactions may occur with a higher incidence in recipients who have a particular clinical condition and be more likely to occur as a result of the effects of another medicine or clinical treatment.

NZBS supplies a form - Notification and Investigation of Adverse Transfusion Reaction - which is used to record the details of adverse reactions. Full and accurate reporting of all adverse reactions is essential. This form is available from all Blood Banks or from the Transfusion Nurse Specialists. On the reverse of this form are Guidelines for the Management of Adverse Transfusion Reactions which are provided to assist clinical staff in the immediate care of the patient. If the reaction is serious, clinical advice is always available from the NZBS Transfusion Medicine Specialists and their contact numbers can be obtained from the Blood Banks.