New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

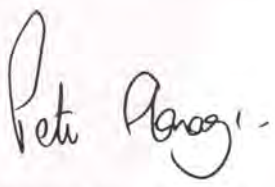
The transfusion of blood and blood products is an accepted part of modern medicine. Considerable efforts are made to ensure that the products provided for patients are safe and effective. Blood is however a biological fluid and safety can never be guaranteed. The risks associated with modern transfusion are however small in comparison to risks in everyday life and indeed to medical practice in general.

New Zealand Blood Service was established in 1998 and given responsibility for the provision of safe and effective blood services to New Zealanders. During 2001 NZBS will be introducing two new major safety initiatives. Nucleic Acid Amplification Technology (NAT) testing of fresh components for HIV and Hepatitis C virus will further reduce the risk that these viruses will be transmitted by transfusion in New Zealand. Universal Leucodepletion is being introduced as part of a package of risk reduction measures to reduce the risk that variant CJD (vCJD) might be transmitted by transfusion.

The risk of transmission of vCJD by transfusion remains theoretical. It appears however that this new threat to blood safety might considerably change the practice of blood transfusion. A number of countries, including New Zealand, have responded to the perceived threat by introducing restrictions on blood donation (the UK deferral) and universal leucodepletion. These measures aim to reduce, but not necessarily eliminate, the risk of transmission. Increased interest is now being devoted to ensuring that transfusion is used appropriately. A number of countries, including Australia, have established major guideline initiatives with the aim of avoiding inappropriate use of blood products. Similar initiatives are being considered here in New Zealand.

This newsletter provides a forum for discussion of topical issues relating to blood transfusion. The newsletter has been developed by the Transfusion Specialists within NZBS. Its aim is to provide information in a timely manner to ensure that clinicians are aware of important developments relating to blood in New Zealand.

The newsletter will be produced on a quarterly basis. Feedback on the initiative will be welcome and should be directed to Dr Susanta Ghosh at the NZBS Waikato Centre.



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National Medical Director

Universal Leucodepletion – On Its Way

Cellular blood components such as red cells and platelets contain a variable number of donor white cells (leucocytes). Even non cellular components such as fresh frozen plasma and cryoprecipitate may contain a small number of white cells. In most instances transfusion of donor white cells is unintended, provides no therapeutic benefit and is associated with a wide rage of potential adverse effects.

Though technology for leucodepletion has been available for more than 30 years only in the 1990's has the concept of high efficiency leucocyte filtration become widely accepted with the availability of filters designed to remove 99.9% to 99.99% or 3 to 4 $\log_{10}$ or more white cells from a unit of red blood cells and platelets.

There has been a growing interest in preventing the adverse effects that can be induced by leucocytes in blood products. These effects can be due to reactions to the leucocytes in red cell and platelet preparations as well as to adverse reactions from inflammatory cytokines produced by leucocytes during storage of units of red cells and platelets. Leucocytes also act as the principal reservoirs and transport vehicle for numerous viral, bacterial and protozoal pathogens. Evidence now exists to support the use of leucodepletion for reducing or eliminating the risk from these blood borne pathogens. For example there is a substantial body of information to indicate that leucodepletion is an effective method for preventing transfusion transmitted CMV infection.

In November 1999, the Ministry of Health identified a requirement that all fresh blood components in New Zealand should be leucodepleted prior to storage. This step is being introduced as part of a package to reduce the theoretical risk that vCJD might be transmitted by leucocytes in blood products in New Zealand.

Leucodepletion brings a number of additional benefits, some of which have been indicated above. These include:

- Reduction of febrile non-haemolytic transfusion reaction.
- Prevention or delay of primary immunisation to human leucocyte antigens.
- Prevention or delay of platelet refractoriness due to alloimmunisation.
- Reduced risk of CMV transmission.

Leucocyte depletion provides other theoretical advantages as well:

- It may reduce the risk of other leucocyte associated blood borne infections, ie less risk of transmission of HTLV I and II and less risk of inadvertent bacterial contamination of blood components.
- It may reduce the risk of peri-operative infection or cancer recurrence by reducing the immunodulatory effects of blood transfusion.
- It may prevent some cases of transfusion related acute lung injury (TRALI).
- It may prevent reperfusion injury following cardiopulmonary bypass.
- It may prevent some of the red cell and platelet storage lesions.

At present bedside filtration for leucodepletion is available for use. However bedside use of leucocyte-depleting filters (rather than leucocyte depletion by the Blood Service soon after the blood was collected) has been associated with precipitous hypotension in some transfusion recipients particularly those on ACE inhibitors. In addition, bedside leucocyte depletion has no effect in reducing the inflammatory cytokines that are released by leucocytes. It is also recognised that bedside filtration may sometimes fail to adequately remove leucocytes due to uncontrolled filtration time and temperature. As white cells degenerate during Blood Bank storage, bedside use of filters is not as effective as pre-storage filtration for removing some infectious agents present in leucocytes.

Pre-storage leucodepletion of whole blood donations will be undertaken at the four NZBS processing centres in Auckland, Waikato, Wellington and Christchurch. The introduction will be a staged process. By the end of June 2001 all blood components manufactured by NZBS will be leucodepleted. Currently, apheresis platelet concentrates prepared at the six main centres, ie the four processing centres, and at Palmerston North and Dunedin, are being leucocyte depleted.

There is some inevitable loss of red cells and platelets during the filtration process. Controlled use of these filters in a laboratory environment will minimise the loss and NZBS will only issue a blood component that meets standards for content. Therefore it is unlikely to influence the number of red cells or platelet units required by a particular patient.

Leucodepleted blood components should be transfused like other blood components using a standard blood giving set. There will be no requirement for continued use of bedside leucodepletion filters after your Hospital Blood Bank starts the routine supply of leucocyte depleted products.

Leucodepleted blood components carry the same risk of haemolytic transfusion reactions and some other allergic and septic reactions as unfiltered blood. Patients will still need to be observed closely during transfusion.

Presentation of the blood components will generally not change. They will be clearly labelled as "leucocyte depleted". The presentation of platelet concentrate will however change. All platelets for adult patients will be provided as an "adult therapeutic dose". These will be produced either by apheresis from a single donor or from recovered buffy coat platelets. Special paediatric platelet concentrates will also be available.

Use Of Anti-D In Pregnancy

Anti-D Immunoglobulin was first introduced for clinical use in New Zealand in late 1968. This treatment had been pioneered by Clarke and others in the United Kingdom. They had shown that IgG class anti-D could suppress immunisation in more than 90% of Rh(D) negative women who were exposed to red cells from an Rh(D) positive baby. This new immunoglobulin product was an exciting development which radically reduced the number of infants affected by haemolytic disease of the newborn. Today we have moved on in time from that discovery and few will remember the enormous impact it made.

Prior to the introduction of Anti-D treatment, about 8% of Rh(D) negative women who gave birth to an Rh(D) positive baby were immunised and made anti-D after their first pregnancy. For those who were not immunised by their first pregnancy, the risk of immunisation was still present in subsequent pregnancies.

The potential problem of haemolytic disease of the newborn varied widely in those affected. Although many cases show only mild haemolysis, others have severe red cell destruction occurring from about mid pregnancy, sometimes with death of the infant before birth. Pioneering work carried out in Auckland by Sir William Liley and his team, which included the Blood Service Staff under Sir Jock Staveley (retired and living in Taupo), led to the world's first intrauterine transfusions. Although this technique saved many badly affected babies, it was prevention of Rh(D) immunisation by use of Anti-D treatment that has been a more important development as it has effectively prevented almost all of the problem of haemolysis in the newborn.

Clinical research on the effect of Anti-D Immunoglobulin has shown clearly that it can reduce the chance for accidental immunisation at birth. However, there are many different circumstances in pregnancy where immunisation by Rh(D) positive red cells might occur. Not all of these have been fully evaluated for the risk of immunisation and the potential value of anti-D. In addition, research studies have not fully evaluated the potential for adverse effects from the anti-D on the developing fetus, particularly early in pregnancy. Experience has suggested that there is no obvious risk for the fetus. This issue requires further study.

When Should Anti-D Immunoglobulin Be Offered To Potential Recipients?

The NZBS Clinical Advisory Group recently prepared Interim Guidelines on use of anti-D in pregnancy. The Guidelines provide a statement for users, including Midwives. In particular, they deal with issues of informed consent and identifies the need for a clinical judgement on whether or not it should be offered in early pregnancy following a complete miscarriage. Copies are available from Transfusion Medicine Specialists and should be available in all Blood Banks. A summary of the indications is given below.

Interim Guidelines For Use Of Anti-D In New Zealand

1. **Postpartum use of anti-D:** An Rh(D) negative woman who has not previously been immunised to make anti-D, who gives birth to an Rh(D) positive infant.

2. **Anti-D for antenatal sensitising events:**

   2.1 An Rh(D) negative woman who has had a: surgical abortion, ruptured ectopic, pregnancy, amniocentesis, external cephalic version.

   2.2 NZBS recognises that definitive studies to support the use of anti-D have not been performed for the following conditions. NZBS also recognises that current international practice supports the use of anti-D for clinically appropriate cases following: threatened miscarriage (before 20 weeks), spontaneous abortion, abdominal trauma, antepartum haemorrhage.

3. **Routine *antenatal* use of anti-D for women who are Rh(D) negative:** This form of treatment has not been widely used in New Zealand, although it is offered in some overseas countries A wider review of the issues surrounding this treatment is needed before a definitive recommendation can be made.

4. **Other indications:** Transfusion of a platelet concentrate obtained from a Rh(D) positive donor.

Informed Consent Leaflets For Patients

NZBS has now prepared a series of information leaflets to assist with informed consent for clinical use of blood products. Most of the leaflets are now in use and the remaining two will appear shortly.

They have been compiled as either single product leaflets - for products usually used on their own, or as multiple product leaflets where products are closely related or tend to be used together. The leaflets deal with:

- Fresh blood components: Red cells/whole blood, plasma, cryoprecipitate and platelets
- Coagulation factor concentrates
- Anti-D Immunoglobulin
- The intramuscular immunoglobulins: Normal, Tetanus, Hepatitis B and Zoster Immunoglobulins
- Albumin (Albumex)
- Intravenous immunoglobulin (Intragam P)

These leaflets are an important means for providing brief and accurate information for informed consent before receiving treatment with blood products.

It is essential that informed consent is regarded as a process and not just an event where a signature is put on a form. The process starts when the medical practitioner or midwife
discusses the treatment with the recipient (or their parent/relative). The leaflets are regarded as being an important contribution to this process.

What Does Informed Consent for Transfusion Involve?

The person should be told whether an intended treatment is orthodox, unorthodox or experimental, and who will provide the treatment. The NZBS information leaflets provide a brief outline of the orthodox indications for use of the respective blood products.

The person should also learn about the expected benefits and the likelihood that they will be achieved in their treatment. Apart from the benefits, the person should hear about the nature of clinically important risks and the chance that they might arise. These topics are well covered by the leaflets which provide a reasonably comprehensive account for lay readers. They should help recipients to think of issues on which they may wish to ask questions.

The overall style of presentation and the material covered has been made as uniform as possible and art work, colour and font selection has ensured a high standard of appearance and readability.

The leaflets should help both intended recipients and many health care professionals by providing access to accurate information on the blood products. In particular, they will provide brief but relevant information on the source of blood products used in New Zealand and the effectiveness of donor screening and testing programmes. These should be of value for dealing with both excessive concerns about safety, and lack of awareness of these issues.

Zoster Immunoglobulin: Source Plasma Supply And Prophylaxis For Chicken Pox

Zoster Immunoglobulin has been in short supply for many years. This blood product presents unusual problems for maintaining an adequate supply of plasma from which it can be made. Most of the plasma has come from older individuals who have suffered a recurrence of infection with the Varicella-zoster virus. They have not usually been regular blood donors

The virus that causes chicken pox normally remains in the body after an acute infection. It takes up residence in nerve cells. Many years later it may re-emerge when the person is 'run down'. The new episode of infection affects a localised area of skin supplied by infected nerve cells. This secondary or recurrent infection is called 'shingles', or herpes zoster.

Until recently, many people who experienced a relapse of the varicella-zoster virus developed relatively high titres of antibody against the virus. With development of anti-viral medicines, patients suffering an outbreak of shingles have had the infection partly suppressed and most have not developed antibody titres that are sufficiently high to provide source plasma for Zoster Immunoglobulin.

NZBS have responded to the problem of reduced supplies of zoster plasma in two ways. Firstly, the titre of antibody against varicella-zoster virus in Intragam-P is now routinely assessed by CSL Bioplasma. This information allows us to calculate the dose of Intragam that is required to give protective treatment against chicken pox infection. Secondly, as a temporary measure, it has been possible to obtain a small stock of Australian Zoster Immunoglobulin to ensure continuity of supply in NZ.

By June 2001 a new supply of Zoster immunoglobulin will become available. This has been produced from New Zealand plasma. The product will be virally inactivated to further improve viral safety.

Efforts are continuing to try to maintain adequate production of source plasma for this scarce product but it is not proving easy. Other strategies for finding suitable donors are also being considered.

Adverse Reactions To Blood Products

Adverse reactions to blood products are not common but may be caused by a wide range of possible mechanisms. The NZ Blood Service aims to assist clinical users by providing clear information on the use of blood products and the investigation and management of any adverse reactions.

Currently a new form for notifying adverse reactions is being prepared and should be available within the next few months. The form will include a prompt list of signs and symptoms to be monitored when an adverse reaction occurs. The form also includes recommendations for evaluation and management of adverse reactions.

The notification of adverse effects of transfusion is the responsibility of Users, the form will be recommended to District Health Boards and Private Hospitals for adoption as a standard local form. As in the past, all adverse reactions should be notified to the local Blood Bank that supplied the product. Reactions should not be notified to CARM as this will lead to unacceptable delay in investigation. The NZ Blood Service will provide CARM with summary updates of all relevant notifications.

Where an adverse reaction occurs to a fractionated blood product, ie albumin, immunoglobulin or a coagulation factor concentrate (products supplied in glass bottles or vials) the reaction should be notified on the new notification form recommended by NZ Blood Service. The local Blood Bank will then seek any additional information needed for evaluation of the reaction.

As is usual practice, when any moderate or severe reaction occurs the transfusion should be stopped immediately and your local Blood Bank notified. Transfusion Medicine Specialists are available in the six main Centres to assist with any complex or severe problems.

If You Require Information On Transfusion Related Issues You Can Contact a Transfusion Specialist. Contact details are shown below

Blood Centre	Telephone
Auckland	09 523 5733
Waikato	07 839 3679
Palmerston North	06 350 8013
Wellington	04 385 5913
Christchurch	03 343 9040
Dunedin	03 474 7926

Intravenous immunoglobulin available in New Zealand

During 2000 CSL Bioplasma ceased manufacture of Intragam. This product has been replaced with a new intravenous immunoglobulin product, Intragam P.

Intragam P, like its predecessor, is manufactured from plasma donated in New Zealand. The new product is subjected to an additional specific viral inactivation step, liquid pasteurisation, and is also purified by chromatography. The product is now available from all NZBS sites and DHB Blood Banks.