

BLOOD ISSUES

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A Transfusion Medicine Newsletter

Supply of Anti-D Immunoglobulin

The current production levels of Anti-D Immunoglobulin manufactured by CSL Bioplasma from the plasma collected from New Zealand donors are insufficient to ensure continuity of supply and for some years now New Zealand has been dependent on a commercial supply of Anti-D Immunoglobulin to supplement supplies. This situation is currently under review and NZBS plans to increase local collection of Anti-D plasma. It will however take some time to achieve self sufficiency.

WinRho™ which is a commercial product manufactured by Cangene Corporation from paid North American donors has been used to supplement the New Zealand product and in recent years CSL Bioplasma has sourced WinRho™ for NZBS. This arrangement changed during 2006 with Baxter Healthcare becoming the sponsor for WinRho™ in New Zealand. Anti-D Immunoglobulin manufactured by CSL Bioplasma is cheaper to produce than the current purchase price of WinRho™ and historically a single NZBS charge has applied irrespective of the product type.

CSL is a major international provider of plasma fractionation services that includes the ownership of a number of collection sites in the United States. Anti-D plasma has been sourced from one of these sites and has been manufactured into Anti-D Immunoglobulin for NZBS. The product is registered for distribution by Medsafe and it is now available in New Zealand.

On 1st January 2007 NZBS introduced a two tier charging system for Anti-D Immunoglobulin with WinRho™ continuing to be supplied at the current price, reflecting the purchase cost of the product from Baxter and the CSL product being charged at a lower rate irrespective of the donor plasma source. NZBS will preferentially issue both CSL manufactured products in an endeavour to reduce overall costs whilst maintaining access to high quality Anti-D Immunoglobulin. In the event however that WinRho® is specifically requested then this product will be provided.

The differential features of the Anti-D Immunoglobulin-VF product sourced from US plasma donors are clearly outlined in the patient information leaflet and product labeling in the following manner:

- The carton label states "this product is made from remunerated donors from the USA"
- The colour band on the carton and vial is pale green
- The hyphenated suffix - VF has been added to the trade name
- The patient information leaflet identifies that Rh(D) Immunoglobulin is prepared from plasma obtained either from NZ voluntary or USA remunerated donors

There are a number of other changes that CSL Bioplasma has made to the patient information leaflet to provide

consistency with the wording of the Australian Product Information leaflet and these changes have been approved by the New Zealand regulator (Medsafe). All other aspects such as indications for use, route of administration, dose and shelf life are the same as the Rh(D) Immunoglobulin product which is manufactured from plasma given by New Zealand donors.

The NZBS informed consent leaflet Your Guide to Anti-D has been updated and is provided with each vial of Rh(D) Immunoglobulin that is issued from the Blood Bank. This will ensure that recipients of the product are fully informed about the nature of the product when consent for the administration of the blood product is obtained by the Lead Maternity Carer. Should you have any questions relating to Rh(D) Immunoglobulin-VF sourced from American donors or require additional copies of the NZBS informed consent leaflet, please contact the Transfusion Medicine Specialist or Transfusion Nurse Specialist in your area.

Availability of Zoster Immunoglobulin

Supplies of Zoster Immunoglobulin are currently very low and product has been purchased from the Australian Red Cross Blood Service to supplement NZBS stocks. The shortage of Zoster Immunoglobulin has resulted from poor collection levels of plasma with high titre Varicella-Zoster antibody. Donors with a recent history of chicken pox or shingles are screened for the antibody but the increasing use of Acyclovir often leads to a reduced immune response and less plasma is sourced using this approach. NZBS plans to introduce routine screening of plasmapheresis donors and although this method of obtaining plasma has had a low yield in the past it should enable supply problems to be prevented in the future. Unfortunately the amount of stock available from ARCBS does not enable NZBS to meet all clinical demand in the short term.

Intragam P has a significant level of Zoster specific antibody activity and is a suitable alternative in a proportion of patients who require prophylactic cover following Varicella-Zoster contact. CSL provide information on the level of Varicella-Zoster antibody in each batch of Intragam P. This enables NZBS to easily identify the appropriate volume of Intragam P required to provide a similar level of Zoster antibody to that provided by the Zoster Immunoglobulin product. In general this will work out at about 20ml of Intragam P per vial of Zoster Immunoglobulin. This approach was used by NZBS in 1999 and enabled NZBS to maintain clinical access to Zoster prophylaxis whilst conserving supplies of the specific immunoglobulin.

The use of Intragam P is cost effective. Currently a 200IU vial of Zoster Immunoglobulin costs \$367.21. Intragam P (50ml) costs \$266.26 and is equivalent to 2.5 vials of the Zoster Immunoglobulin.

Haemovigilance

NZBS released its first national Haemovigilance report during 2006. This article provides an overview of the processes used for Haemovigilance in New Zealand. An electronic copy of the full Haemovigilance report for 2005 can be found in the Haemovigilance section of the NZBS website www.nzblood.co.nz. A printed copy can be obtained by contacting the National Haemovigilance Office on 09 523 5744 or haemovigilance@nzblood.co.nz.

The provision of safe transfusion therapy is a basic requirement of medical care. Despite major advances in viral and bacterial detection and the subsequent reduction in risk of transfusion transmitted infections there are still significant risks associated with transfusion.

The Council of Europe (CoE) has an expert committee which is responsible for drafting the 'Guide to the preparation, use and quality assurance of blood components' recognised internationally as a gold standard for blood services. NZBS has a commitment to the principles of the CoE and has observer status on the CoE 'Committee of Experts on Quality Assurance in Blood Transfusion Services'. NZBS has adopted the CoE definition of haemovigilance which is '*the organised surveillance procedures related to serious adverse or unexpected events or reactions in donors or recipients and the epidemiological follow up of donors*'.

The information provided by haemovigilance contributes to improving the safety of blood collection and transfusion by:

- providing the medical community with a reliable source of information about adverse events and reactions associated with blood collection and transfusion;
- indicating corrective measures required to prevent the recurrence of some incidents or dysfunctions in the transfusion process;
- warning hospitals and blood establishments about adverse events and reactions that could involve more individuals than a single recipient, including:
 - those related to the transmission of infectious diseases and those related to blood bags, solutions or blood processing

Co-operation between NZBS and Clinical Staff

Reporting and analysis of adverse events and reactions associated with transfusion requires close co-operation between the clinical setting where transfusion takes place, the hospital blood bank that issues the transfused blood component and NZBS who collects manufactures and distributes the blood component. This co-operation is essential to ensure a complete investigation of an adverse event, transfusion reaction or transfusion error.

Each hospital blood bank has a nominated 'Transfusion Safety Officer' (TSO) who ensures that a completed notification form is forwarded to NZBS. The blood

banks associated with the six NZBS centres also have a Transfusion Nurse Specialist who follow up reported events and provide education to those involved in the transfusion process.

Trends in Blood Product Usage in New Zealand

NZBS monitors the activity levels and trends in clinical demand for the blood components and products that it supplies. Overall demand for red cells and fresh frozen plasma (FFP) components during the period 2002-2005 has remained reasonably stable. Demand for platelet concentrates has been variable and the demand for Intragam P has increased.

NZBS Haemovigilance Programme

The NZBS Haemovigilance programme for notification of transfusion-related adverse events was formally introduced by NZBS on 1 May 2005 following an initial four-month pilot programme at three North Island hospitals. Modelled on similar schemes in the UK and Ireland the programme collects data on the incidence of **all** types of transfusion-related adverse events. 13 categories of event have been selected including incorrect blood components or products transfused, immune and cardiovascular complications of transfusion, transfusion transmitted infections and events due to specific equipment or components.

Definitions for the event categories are derived from those used by the United Kingdom Serious Hazards of Transfusion scheme (SHOT) and from the European Haemovigilance Network (EHN) 'Working Party on definitions of adverse transfusion events (ATEs)' released in 2004.

Events are reported using a dedicated form, copies of which are held by all blood banks in New Zealand. Depending on the type and severity of event being reported there are specific follow-up questionnaires for obtaining more detailed information about the event including the patient outcome and sequelae. Each reported incident is categorised as serious or non-serious with serious events requiring further discussion with a NZBS Transfusion Medicine Specialist (TMS).

A serious event is defined as any adverse event that:

- requires hospitalisation or a prolonged hospital stay
- results in persistent or significant disability or incapability
- necessitates medical or surgical intervention to prevent permanent damage or impairment of a body function
- is associated with severe temporary or permanent morbidity and/or mortality

Consideration also needs to be given as to the likelihood that a reported serious adverse event or reaction is causally related to the blood component or product being transfused. This assessment of *imputability* is based on the CoE classification shown in table 3.

Table 3: Imputability Assessment Scale

Imputability Scale		Explanation
NA	Not assessable	When there is insufficient data for imputability assessment
0	Excluded	When there is conclusive evidence beyond reasonable doubts for attributing the event to alternative causes
0	Unlikely	When the evidence is clearly in favour of attributing the event to causes other than the blood or blood components
1	Possible	When the evidence is indeterminate for attributing the event either to the blood or blood components or alternative causes
2	Likely, probable	When the evidence is clearly in favour of attributing the event to the blood or blood components
3	Certain	When there is conclusive evidence beyond reasonable doubt for attributing the event to the blood or blood components

Traceability of Blood Components

Traceability is a prerequisite for haemovigilance and is defined as the ability to trace each individual unit of blood or blood components from the donor to its final destination. Traceability provides information on the total number of:

- patients that have been transfused;
- blood units or components that have been used;
- blood donors that have provided the transfused blood units or components. This information assists with the calculation of the incidence of adverse events and reactions and enables NZBS to estimate risk. The number of adverse events and reactions, over a given time period, will help in identifying critical issues within the process.

Traceability also covers cases in which the blood unit or component is not transfused to a patient, but is used for the manufacturing of medicinal products, for research and investigational purposes, or for disposal. The essential element for traceability is a unique identification numeric or alphanumeric code for each donation, with a subsidiary code for each component prepared from that donation. This unique identifier is linked with data identifying both the donor and the recipient and enables NZBS to identify all patients transfused with a particular donor's blood or all donors who donated the blood components.

Using this system the following data is available:

- personal data uniquely identifying the donor and providing a means to contact him/her;
- the site where the blood collection has been carried out;
- the date of the donation;
- the blood components produced;

- the blood bank to which the blood component has been distributed;
- the hospital and the ward to which the blood component has been issued for transfusion;
- the date and time of issue;
- the final fate of the unit;

Confirmation that the blood component was transfused to the patient for whom it was issued is needed and currently, proving the link between donor and patient requires verification in the patient's notes that the blood component had been transfused.

Adverse Reactions in Donors

Adverse reactions in donors are either observed during donation by collection staff or reported to the collection centre by the donor after they have left the collection venue. Initial care and advice to the donor as well as follow-up of the reaction is provided by an NZBS Registered Nurse. A Medical Officer reviews the adverse reaction report and provides clinical advice and support if required. Reports and statistics are collated by individual NZBS sites and on a national basis. The following categories of adverse reactions are currently used by NZBS:

- Faints
- Soft tissue/tendon damage (including bruises and haematomas)
- Arterial puncture
- Nerve damage
- Thrombophlebitis
- Injury (occurring as the result of an accident at the session, or in the vicinity of the session, or otherwise related to donation and may include, for example, a fall resulting in head injury or a car accident).
- Medical/fits (including symptoms and/or signs not otherwise differentiated such as a fit, stroke or a suspected myocardial infarct)
- Other events (including skin infections and allergic reactions)

Infectious Disease Screening

Donor epidemiological data relating to the number of donations that are confirmed positive for Hepatitis B, C and HIV is collected nationally by NZBS. This data is also reported annually to CSL Bioplasma (the plasma fractionator) as part of the regulatory process associated with manufacturing human-derived plasma products, and in particular to meet the scientific data requirements for the plasma master file (PMF).

Bacterial Monitoring of Platelet Concentrates

Bacterial contamination of blood components was first recognised as a complication of transfusion over 60 years ago. Sources of contamination include donor skin, donor bacteraemia, faulty blood collection or contamination during blood processing. The organisms detected are usually aerobic and those most frequently implicated in clinical cases of transfusion-associated sepsis include *Staphylococcus*, *Streptococcus*, *Bacillus cereus*, *E. coli*, *Salmonella* and *Serratia*.

A variety of strategies to reduce bacterial contamination are used by the NZBS. These include detailed donor screening with deferral of those identified to be at risk of bacteraemia, augmented disinfection of the venepuncture site to reduce the entry of skin flora into the unit and diversion of the first 10-40ml of blood collected prior to collection of the unit. This latter approach has been shown to significantly reduce the rate of bacteria contamination and was introduced by NZBS during 2002.

NZBS commenced a pilot in 2004 to determine the bacterial contamination rate of platelet concentrates in NZ. Platelet units were initially sampled on day 2 post-collection (day of collection = day 0) using non-destructive sampling methods so as to have no impact on the availability of platelets for clinical use. Similarly any units originally sampled on day 2 that had not been issued for use by day 5 (expiry) were held for a further two days until day 7 post-collection and retested. All samples were tested using the BacT/ALERT 3D automated microbial detection system. Any initially positive results were further investigated and all components associated with the positive sample traced and any not already transfused placed into quarantine. Samples of the implicated components were sent to an accredited microbiology laboratory for gram stain, culture and identification of any bacteria present. During 2005 all four NZBS manufacturing sites Auckland, Waikato, Wellington and Christchurch participated in the study with Auckland and Christchurch participating for the full year, Wellington for nine months and Waikato for ten months.

In line with Council of Europe requirements, the NZBS has now introduced routine bacterial culture of platelet components as a process control measure. Currently about 50% of all platelet products are cultured using the scheme identified above.

Adverse Reactions To Fractionated Products

Large volumes of fractionated plasma products are used in the treatment of a wide range of conditions. Although rare, patients do occasionally experience reactions to these products and these are notified both to NZBS and the manufacturer of the implicated product. The New Zealand Blood Service national process for reporting adverse reactions to fractionated blood products has been in operation for six years.

CSL Bioplasma manufactures 10 fractionated blood products for NZBS using plasma from New Zealand donors. These products are – Albumex®, Intragam®, AHF (now Biostate®), MonoFIX-VF™, Thrombotrol, Prothrombinex™, Hepatitis B Immunoglobulin, Rh (D) Immunoglobulin, Normal Immunoglobulin and Zoster Immunoglobulin. During 2005, CSL Bioplasma supplied the Cangene product WinRho-SDF to meet the demand for Rh (D) Immunoglobulin for New Zealand patients. Other products that are supplied by NZBS include the commercial products, Hyper HepB, Berinert P and Fibrogammin.

DHB Clinical Oversight Programme

The NZBS 'DHB Clinical Oversight Programme' was introduced on 1 January 2005. It was developed in response to the increasing number of requests from DHBs for specialist transfusion medicine support (both clinical and technical) needed to meet the requirements of NZS/ISO 15189:2003 'Medical Laboratories – Particular Requirements for quality and competence'. Outside of the six NZBS-operated blood banks the requisite support for hospital blood banks and laboratories particularly in the smaller provincial centres had become increasingly scarce, and where available, inconsistent. The components of the programme are as follows:

- Clinical Audit Of DHB Transfusion Policies and Procedures - One clinical audit every two years of hospitals where transfusions are carried out, encompassing blood storage and refrigeration, informed consent, dispensing systems and clinical records documenting transfusion and traceability.
- Site Visits - One formal site visit per year (to non-NZBS blood banks or laboratories where pre-transfusion testing is performed) intended as a collaborative review of systems and processes to promote best practice. Wherever possible a TMS attends DHB Hospital Transfusion Committee meetings or education sessions. 24 hour, 7 day access to clinical advice is also available via the NZBS TMS on-call roster.
- Regional Meetings/Seminars - Three 'customer focussed' meetings per year are held by each of the four main NZBS centres (Auckland, Waikato, Wellington and Christchurch).
- Education - Developing and maintaining appropriate educational and training resources.

The programme is now well established and is working well. During 2005 more than 20 hospitals received site visits and/or clinical audits. Regional meetings were hosted by the four main NZBS centres.

Clinical Audits of Component and Product Usage

NZBS employs six Transfusion Nurse Specialists (TNS) with one situated in each of the six NZBS blood banks. Each year audits encompassing the six DHBs and, in some cases, other DHBs, are undertaken by the TNS team, co-ordinated by a NZBS TMS, on different aspects of transfusion medicine. In addition local audits are performed, some of which act as pilots for larger collective audits. In the last two years, five collective audits have been undertaken, looking at: overnight transfusion practice, cryoprecipitate use and non-use, Intragam P use, irradiation of cellular blood components and platelet use respectively. These audits have concentrated on issues around clinical practice as well as appropriateness of use.

Reports of each audit are provided to the hospital transfusion committees in draft form for comment, to allow the DHBs an opportunity to provide input into the audit conclusions. Final reports are circulated to the hospital transfusion committees and CEOs of all 21 DHBs. This partnership between NZBS and DHBs has enabled audit work to provide useful insight into blood component and product use in New Zealand.