New Zealand Blood Service
The gift of life

BLOOD ISSUES

November 2002, Issue 5 A Transfusion Medicine Newsletter

Editorial

During October this year the NZBS Clinical website went live. In setting this up our aim has been to provide information to both potential recipients of blood and blood products and to Health Care professionals. An open approach has been adopted with all documents freely available to the public.

All the information which is currently in the NZBS Clinical Compendium is available on this site, together with additional features such as the Clinical Newsletter, leaflets and donor information.

The website can be located at www.nzblood.co.nz, and the Clinical section of the website can be accessed by clicking on the *About NZBS* section of the menu and then clicking on *Clinical Transfusion Medicine Services*. The following menu will then appear:

- Adverse Reaction Reporting and Management
- Clinical Newsletter
- Information for Donors
- Information for Health Professionals - Policies
- Information for Health Professionals - Medicine Data Sheets
- Information for Potential Recipients of Blood and Blood Products
- Links

The site will be regularly updated and our aim is to ensure timely access to NZBS initiatives in the area of clinical transfusion medicine. We are currently investigating the feasibility of the site being provided on a CD-ROM, and hopefully this may be available early next year.

This edition of the newsletter contains information on haemolytic reactions encountered following transfusion of Intragam P, including a recently issued Medical alert. Haemolytic reactions are a recognised complication of treatment with any Intravenous Immunoglobulin product and the number of reports of this type of reaction received by NZBS appears to have increased during the last year. NZBS has become aware of this issue following receipt of reports of reactions collated as part of our Adverse Reaction Monitoring programme. Information on this is available on the website. Medsafe have recently confirmed that the NZBS system will be the main mechanism for reporting of reactions to blood products in New Zealand. NZBS will provide quarterly reports to Medsafe outlining any issues or trends arising. This will in time become part of a wider Haemovigilance initiative.

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National Medical Director

Transfusion-Associated Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is a frequent complication of allogeneic bone marrow and peripheral blood stem-cell transplant. GVHD occurs when donor haematopoietic stem cells recognise human leukocyte antigen (HLA) in the recipient as foreign and react to it. Diarrhoea, abnormal liver function, characteristic skin rash and fever are the main clinical features of this condition.

In the 1960s it was recognised that a similar condition may develop following transfusion of cellular blood components containing viable T-lymphocytes. Since then, this transfusion-associated GVHD (TA-GVHD) has been recognised as a distinct disease entity. It is often associated with pancytopenia due to marrow aplasia, is resistant to almost all immunosuppressive therapy and has a high mortality.

Signs and symptoms of TA-GVHD usually appear 8 to 10 days after transfusion and are initially the same as GVHD. However marrow aplasia follows soon after, leading to death in about 3 to 4 weeks after transfusion.

TA-GVHD is sometimes difficult to differentiate from severe drug reaction and many viral infections. Only characteristic pathological changes in liver, skin and bone marrow together with demonstration of donor lymphocytes in recipient's circulation will establish the diagnosis.

Patients at risk of developing TA-GVHD

Early cases of TA-GVHD were reported in patients with congenital immunodeficiencies, in patients with haematological and other malignancies and in newborns with erythroblastosis foetalis, but it has not been reported in patients with acquired immunodeficiency syndrome (AIDS).

The true incidence of TA-GVHD is not known but is estimated to occur in 0.1% to 1% of patients with lymphoproliferative disease or haematological malignancies. The table below lists the patient groups at risk of developing TA-GVHD.

Definite Risk

- Allogenic and Autologous Bone Marrow or Peripheral Blood Stem Cell Transplant recipients
- Aplastic anaemia patients receiving immunosupressive therapy
- Hodgkin's disease patients
- Recipients of blood products donated by relatives
- Recipients of intrauterine transfusion and all subsequent transfusion/neonatal exchange transfusion
- Patients with congenital cellular immunodefciency

- Recipients of HLA matched platelets
- Patients receiving purine analogues i.e. fludarabine, cladribine
- Recipients of granulocyte transfusion
- Newborns with erythroblastosis fetalis

Possible Risk (cases which have been reported)

- Premature/low birth weight infants
- Patients with Lymphoid malignancies
  - T-Cell malignancies
  - B-Cell malignancies with lymphopenia ($<0.5 \times 10^9$/L)
  - Therapeutic antibodies against T cells
- Patients with Non-Lymphoid malignancies
  - Acute Leukaemia
  - Chronic Myeloid Leukaemia
  - Patients with lymphopenia ($<0.5 \times 10^9$/L)

No risk (no reported cases)

- AIDS patients
- Patients with congenital humoral immunodeficiency
- Thalassaemia patients
- Patients with haemophilia

Prevention and Management

Treatments which are commonly used to treat GVHD are rarely effective in the treatment of TA-GVHD. There is some anecdotal report of response to treatment but there is not enough information to formulate a treatment strategy. Prevention is therefore of paramount importance.

Since T-lymphocytes are responsible for TA-GVHD, leucodepletion of blood components can theoretically be used to prevent TA-GVHD, but at present the minimum number of T-lymphocytes required to mediate TA-GVHD, is not known.

TA-GVHD has also been reported in recipients of leucodepleted blood components and this information would suggest that current leucodepletion procedures do not completely prevent TA-GVHD.

Blood components can be subjected to gamma irradiation to prevent TA-GVHD in patients who have a high risk of developing TA-GVHD. This inactivates the T-lymphocytes while preserving the function of other blood cells.

Gamma Irradiation of all blood components is not indicated because of the very low risk of immunocompetent patients developing TA-GVHD following the transfusion of blood from unrelated donors. Gamma irradiated blood can be transfused safely to all patients.

The New Zealand Blood Service currently recommends irradiation of blood components at 25 Gy, with no area receiving less than 15 Gy. This dose is considered sufficient to inactivate T-lymphocytes.

West Nile Virus – A Transfusion Transmitted Infection?

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 disease was identified in the United States in the New York area. Over the last few months there has been a significant increase in the number of cases occurring in the US. In addition cases have been identified over a much wider geographical area in both the United States and Canada. This has led to increasing concern within the US. The possibility that the infection might be transmitted by transfusion has resulted in considerable debate in the US.

West Nile virus is an enveloped virus of the flavivirus family. The virus is maintained in an enzootic cycle involving culicine mosquitos and birds. When environmental conditions are favourable sufficient numbers of "ridge vector" mosquitos - mosquitos that bite both birds and humans - become infected in late summer and then pose an infection threat to humans. In the US this occurs in late summer. In tropical climates it can occur year round.

The incubation period of West Nile virus probably ranges from 3-14 days. Most human infections are not clinically apparent. 1 in 5 infected persons develop a mild febrile illness, 1 in 150 develops meningitis, encephalitis or both. Advanced age, over 50 years, is by far the great risk factor for severe neurologic disease, long term morbidity and death. More recently, a polio-like paralytic syndrome has been described.

In August this year a case of probable transmission from an organ donor was reported. This led to close scrutiny for possible transfusion transmitted infection. A number of cases are currently being investigated by the US Center for Disease Control (CDC). The evidence clearly signals that this infection can, and almost certainly, has been transmitted by transfusion. Authorities in the US are actively investigating possible mechanisms to reduce the risk of this occurring. A number of strategies, including the possibility of PCR testing, are being investigated.

To date there have been no cases of West Nile virus infection reported in New Zealand. The culicine mosquito is not present in the country. The possibility however that individuals who have recently visited the United States and been bitten by mosquitos which might carry the infection cannot be excluded. Should such an individual donate blood then this could be transmitted by transfusion. The risk currently appears remote but will be closely monitored.

In New Zealand, if necessary, the risk could be eliminated by excluding recent travellers to the US for a period of two weeks following return. This strategy would essentially eliminate the risk of this occurring. Current data do not however indicate that such action is necessary or appropriate. In particular, the impact of excluding such donors, in terms of numbers, is not known.

The risk of transmission by transfusion will be limited to fresh blood components. Fractionated plasma products currently available include dedicated viral inactivation steps during their manufacture. These are highly effective in removing enveloped viruses such as West Nile virus. West Nile virus is an emerging transfusion infection of significant concern in the United States, particularly during the late summer period. At this stage the risk to the blood supply in New Zealand appears to be very small indeed. The issue will be closely monitored.

Apheresis

Apheresis means to take away. In transfusion practice it means the removal of one or more constituents of blood from the body, in most instances by mean of an automated cell separator. The cell separators contain a centrifuge or a filter which separates the various blood components e.g. red cells, platelets, white cells, plasma. The required component can be removed from the blood while everything else is returned to the patient or the donor. In some instances specialised techniques can be used to remove only the offending antibodies or lipids from the patients.

Donor Apheresis

Many of our donors make a commitment to donate plasma every few weeks. As the donors do not lose red cells in the process it is possible for them to donate much more frequently than whole blood donors do. Plasma from many of these donors can contain high levels of particularly useful antibodies and provide plasma for making hyperimmune or specific immunoglobulins like Hepatitis B Immunoglobulin, anti-tetanus Immunoglobulin and anti-D Immunoglobulin.

Similar techniques can be used to obtain a large platelet donation, which is sufficient for one or more adult doses. This reduces the number of donors that the patient is exposed to and thus reduces the risk of transfusion transmitted infections. Plateletpheresis is also a valuable process for obtaining platelets that are suitable for patients who have developed antibodies to platelets and for whom specially selected platelets are required. At present about 50% of the platelets used in New Zealand are collected using the apheresis procedure.

Therapeutic Apheresis

Apheresis can be used to remove harmful proteins, lipids or drugs or excess constituents such as platelets, white cells or red cells.

Most of the patients are treated by plasmapheresis (often called 'plasma-exchange' because plasma is replaced with plasma or a plasma substitute) with the intention of removing offending antibodies or a high level of abnormal proteins or lipids.

Guillian-Barre syndrome, hyperviscosity due to myeloma protein, Myasthenia Gravis and Familial Hypercholesterolaemia can all be managed by this procedure. In most cases 4% albumin solution is used as a replacement fluid but Fresh Frozen Plasma or Cryosupernatant is used in cases of Thrombotic Thrombocytopenic Purpura. Plasma-exchange not only removes harmful constituents of plasma but beneficial ones as well. However, selective removal of some of the harmful materials is possible by the use of selective absorbent columns.

Some patients with very high white cell counts or platelet count and hyperviscosity syndrome can be managed by using cell separators. Cell separators can remove a large number of white cells or platelets very quickly without depleting other blood components.

Peripheral Blood Stem Cell (PBSC) Harvest

Similar techniques can be used to harvest stem cells from patient's or donor's blood. The stem cells are frozen and then returned intravenously after the chemotherapy or radiation therapy is completed. Once transplanted the stem cells usually take less than three weeks to repopulate the blood, compared to a month or more for a bone marrow transplant. This means that there is less risk or infection or bleeding during the recovery from the transplant.

Complications

Apheresis is a relatively safe procedure and can be used for patients of all ages provided good venous access is available. Occasionally, hypotensive attack or cardiovascular instability is seen but these complications are rare in experienced hands. Anaphylactic reaction to replacement fluid has been reported, but is also a rare occurrence.

National Immunohaematology Quality Assurance Programme

The New Zealand Blood Service is introducing its 'National Immunohaematology Quality Assurance Programme' (NIQAP) for use by blood transfusion laboratories throughout New Zealand.

NIQAP will replace both the long running 'National Immunohaematology Proficiency Survey (NIPS)' provided by the blood transfusion laboratory at Taranaki Base Hospital and the 'Red Cell Serology Survey' provided by NZBS Auckland.

It is believed that NIQAP will meet the external quality assurance needs of New Zealand blood transfusion laboratories and their staff. With this in mind a project team of representatives from both NZBS and District Health Board blood transfusion laboratories has been formed with the aim of ensuring that NIQAP not only meets its goals but continues to evolve in a dynamic way.

The annual programme initially consists of three exercises (or surveys) each with a specific testing or technical focus. Each exercise aims to challenge participants by providing specimens and clinical scenarios which mimic typical blood transfusion requests or processes as faced by the average laboratory during routine pretransfusion testing. In this way

laboratories can assess their performance (and that of individual staff members) not only against the expected results but also other laboratories throughout the country.

Each exercise will usually highlight a technical issue faced by blood transfusion laboratories, which will then be explored through the expert commentary provided with the post exercise report. In this way it is hoped to stimulate awareness of, and debate around, the performance and practice of pretransfusion testing across New Zealand and internationally.

With the first exercise scheduled for early October 2002 there is already widespread support for this programme with around 120 enrolments representing a wide cross section of laboratory staff involved in blood transfusion testing in Private, DHB and NZBS Laboratories.

Intragam® P – Risk of Haemolytic Reactions

In the past twelve months, the New Zealand Blood Service has received five reports of haemolytic, or potentially haemolytic, reactions following administration of high dose Intragam® P. Clinical users are reminded that Intragam® P is a pooled plasma product and as such contains the ABO blood group antibodies, anti-A and Anti-B. The product datasheet identifies the possibility of both positive antiglobulin tests and red cell haemolysis occurring in association with high dose treatment.

The frequency of incidents currently being reported in New Zealand appears to be higher than expected. However in the same period, this has not been observed in other countries where Intragam® P is distributed, including Australia.

The New Zealand Blood Service has discussed the reports with CSL Bioplasma and Medsafe. The episodes are not related to any single batch. The release criteria for batches of Intragam® P require that they meet the European Pharmacopoeial Standard with respect to titres of anti-A as well as anti-B and anti-D.

This Medical Alert is brought to your attention so that you can review treatment for patients receiving this product, and where appropriate, can monitor for potential adverse effects.

The affected recipients have been treated with Intragam P for the following conditions; Kawasaki's disease, immune thrombocytopenic purpura (ITP) and Guillain Barre syndrome. They have received Intragam P doses of 1-2g/kg over periods of 1-5 days. The implicated individuals have been blood group A or AB and the fall in haemoglobin level has varied, but in one case required transfusion.

CSL is currently investigating the reports. Whilst this is being undertaken, NZBS recommends that potential recipients of high dose Intragam P should have their ABO blood group determined. Haemolysis, if present, is likely to be observed in the later phases of a treatment course and in the following few days.

Recipients, particularly those who are a Blood Group A, should be monitored during and immediately after each course of high dose treatment, i.e. those receiving doses in the range of 1-2g/kg over short periods of 1-5 days.

Local Transfusion Medicine Specialists are available to provide advice where appropriate.

NZBS is closely monitoring the situation and will ensure that the manufacturer (CSL Bioplasma) and Medsafe, the regulator, are kept informed. Adverse reactions should be reported to your local blood bank who will forward the reactions to NZBS using the established reporting system.

vCJD and Imported Fractionated Blood Products

There is no evidence that fractionated blood products, including Intravenous Immunoglobulins, have transmitted either Creutzfeldt-Jakob disease (CJD) or variant Creutzfeldt-Jakob disease (vCJD).

A number of countries, including New Zealand, have introduced measures to reduce the risk that vCJD might be spread by blood products in the future. This has involved the exclusion as blood donors any people who have spent substantial time in countries where the risk of disease is increased (including the United Kingdom) and also the exclusion of any people who have had a transfusion in the United Kingdom.

The United States and Canada also exclude some potential donors who have lived in Europe.

As a further precautionary measure, the Ministry of Health has asked NZBS to ensure that in clinical circumstances where some patients require access to products other than those manufactured from New Zealand plasma, that this decision made by the prescribing doctor, takes into account all the relevant issues.

NZBS is required to inform the prescribing doctor that the product is an imported product, alert the prescriber to information about the source of the plasma from which the product has been derived and draw attention to the manufacturer's product information sheet.

The following imported fractionated blood products are being supplied in New Zealand via the New Zealand Blood Service.

PRODUCT	PLASMA SOURCE
Sandoglobulin	Netherlands, Germany and Poland
BayHep B	United States
WinRho SDF™	United States and Canada
FEIBA®	United States, Austria, Germany and Czech Republic
C1 Inhibitor TIM 3	United States, Austria, Germany and Czech Republic
Imogam	United States
Fibrogammin P	Awaiting a response from Aventis Pharma