BLOOD ISSUES

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Editorial

This edition of Blood Issues focusses on Fresh Frozen Plasma (FFP) and highlights a number of initiatives undertaken by NZBS in recent months to improve the safety profile and reduce wastage of this product.

During 2006 a total of 20619 units of FFP were transfused to 1883 patients. Use of this component in New Zealand is relatively stable. International studies consistently identify that a significant proportion of transfusions of FFP do not comply with current guidelines. This is a concern since 1 in 56 patients receiving the component will suffer a transfusion reaction. Many of these will be relatively minor, involving allergic reactions such as urticaria. In some cases however more serious adverse events occur. FFP is recognised as a major cause of Transfusion-Related Acute Lung Injury (TRALI).

FFP is commonly used in major bleeding situations. There is a significant lag time between ordering the product and it being available for transfusion. This primarily reflects the time it takes to thaw the component. This delay contributes to a significant level of FFP being thawed and then not required. During 2007 almost 2000 units of FFP were thawed and then discarded. This reflects a cost of over $300K. In October 2007 the shelf-life of thawed FFP was extended from 4 hours to 24 hours. This should reduce the overall level of wastage of this component.

In 2005 the UK introduced a change whereby clinical FFP was only produced from donations given by male donors who had never been transfused. This significantly reduced the rate and severity of TRALI cases reported to SHOT, the UK Haemovigilance system. A number of countries have since adopted this approach. In New Zealand a move to predominant 'male only' FFP will be achieved by the introduction of clinical FFP produced from apheresis donations. More information on this is provided in this newsletter.

It will be several months before the full benefits of these changes are apparent. They do however provide an opportunity to increase the safety and reduce costs associated with the component.

Dr Peter Flanagan
NZBS Medical Director

Introduction of 'Male-Only' Clinical Fresh Frozen Plasma (FFP)

Starting in February 2008, NZBS will be moving progressively to manufacture clinical Fresh Frozen Plasma (FFP) from male donors. This is in line with current international practice and aims to reduce the frequency of Transfusion-Related Acute Lung Injury (TRALI) associated with transfusion of FFP. This initiative is cost neutral for NZBS and will not impact on the charge for the product.

Data from haemovigilance schemes in New Zealand and overseas have demonstrated that more severe cases of TRALI are associated with transfusion of blood components that contain plasma. The main cause of TRALI is believed to be due to transfusion of plasma containing high levels of antibodies directed at antigens on leucocytes. The antibodies may be directed against antigens present on neutrophils (neutrophil specific antigens) or HLA associated antigens that are more widely distributed on cell surfaces. Transfusion of these donor antibodies leads to agglutination of leucocytes in the pulmonary vasculature leading to acute lung injury. Leucocyte antibodies are commonly stimulated by pregnancy or transfusion of components containing leucocytes. The frequency of antibodies will thus be significantly lower in FFP derived from male donors. Data from the United Kingdom and Canada has demonstrated that this approach will reduce the frequency of TRALI cases.

NZBS will move to production of FFP derived by apheresis in order to achieve predominant male only FFP. This approach will bring a number of benefits. Each apheresis procedure will result in three units of FFP. This will provide an opportunity to reduce donor exposure for patients requiring multiple units of product. It will also enable NZBS to increase manufacture of group AB FFP. This can be transfused to patients of any blood group. Combined with the recent extension of the shelf life of thawed FFP, this provides an opportunity to further reduce wastage of the product. It is important to emphasise that these changes will be introduced progressively over the next 12 months. During this period NZBS will also investigate the feasibility of further restricting manufacture to male donors who have not received component transfusions. Possible approaches to limit the risk associated with platelet products are also being investigated.

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Te Ratonga Toto O Aotearoa

Apheresis FFP meets the requirements of the current NZBS specification. Some changes will however be seen:

- The volume of each component might be slightly lower than that of the whole blood derived product. For the majority of patients this should not however influence the number of units required for a standard 12-15 ml/kg transfusion.
- The presentation of the pack will differ slightly from the current FFP product. This reflects the different manufacturer of the apheresis container. The apheresis FFP product will appear identical to the current cryoprecipitate product which is also made from plasma collected by apheresis. This will not lead to any issues when the component is transfused.
- The 3 components produced from each donation will have the same donation number. Each individual component will be distinguished by the component code. This provides full traceability and is the same approach currently used for apheresis platelets. Transfusion of multiple units of FFP occurs more frequently than occurs with platelets and hence the duplication of the donation number will be more visible to the end user. Whilst awareness of this is important, it will not lead to any requirement for changes to local transfusion procedures.

In common with other countries NZBS is adopting a policy of predominant male only FFP. Experience in the United Kingdom has indicated that during periods of high demand it may be necessary to provide FFP from female donors. The use of apheresis derived FFP will reduce the likelihood of this occurring. Nonetheless NZBS will only commit to 100% male only FFP once experience has demonstrated that this can be achieved without any undue disruption to supply.

Multi-Centre Audit of FFP Use

A steady increase in the use of Fresh Frozen Plasma (FFP) has been seen internationally, despite increasing concerns about complications, particularly Transfusion-Related Acute Lung Injury (TRALI), and the lack of evidence for much of FFP's use.

A multi-centre audit was undertaken to investigate the appropriateness of the use of FFP. Sites involved in the audit were Auckland City, Starship, Waikato, Palmerston North, Wellington, Christchurch, Christchurch Women's and Dunedin Hospitals. Each site analysed a minimum of fifty episodes of FFP transfusion. These were assessed against the current NHMRC/ASBT guidelines.

For audit purposes, an episode was defined as each time the participating blood bank issues one or more units of FFP to a patient. The following data were collected for each episode: demographic data, time of infusion, number of FFP units, prescribed rate and actual duration of infusion, the number of red cells, fresh frozen plasma, platelets, cryoprecipitate units, and/or vials of Prothrombinex®-VF transfused in the previous 12 hours, clinical diagnosis, indication for FFP, rate of bleeding, cardiac status, recent Warfarin therapy, relevant co-morbidities, coagulation and blood count test results.

Audit data was collected by the Transfusion Nurse Specialists. Two NZBS Transfusion Medicine Specialists assessed the appropriateness of each episode, based on the NHMRC/ASBT guidelines, the principles of use in bleeding patients, and considering Prothrombinex®-VF as an alternative to FFP.

The six centres collected 335 episodes involving 867 units of transfused FFP. 79% of episodes were assessed as appropriate or probably appropriate. 50% of transfusions were underdosed, even allowing for those transfusions split over time for heart failure. Underdosing varied significantly between DHBs. Warfarin reversal accounted for 18% of episodes but Prothrombinex®-VF use was minimal. Patients transfused FFP for mildly abnormal INR results showed an average of 0.1 fall in INR, despite a full dose of FFP. Excluding transfusions for TTP, and specific coagulation proteins, coagulation testing was conducted in 98.7% of episodes, within an average of 6.7 hours before transfusion. FFP was prescribed for transfusion and transfused in under an hour in 90% and 88% of episodes respectively.

The results of this audit compare well with other countries, with appropriate transfusions reported in 63% and 72% in two separate audits in Australia, 27% in Singapore, 30% in Taiwan, and 62-92% in six audits in the UK. Appropriate dosing was not reported as widely but UK audits ranged from 33-84%. Nevertheless the high level of underdosing is of concern, particularly with the strong association between Transfusion-Related Acute Lung Injury (TRALI) and FFP. While a low dose may be argued as reducing the risk of TRALI, an ineffectual dose confers a risk onto the patient with no or reduced corresponding benefit. The variation between DHBs suggests this may be amenable to education. The low level of Prothrombinex®-VF use and the number of episodes that could have been managed better with vitamin K suggest the Australian Society of Thrombosis and Haemostasis (ASTH) Warfarin reversal guidelines have not been well embraced. FFP transfusions for mildly abnormal coagulation are considered of doubtful value, as demonstrated by the poor fall in INR in response to FFP.

NZBS Plans to Introduce 'Mini-Dose' of Anti-D Immunoglobulin

Current Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) Guidelines identify that a 'mini-dose' preparation of Anti-D Immunoglobulin (250 IU) can be used to provide protection for Rh(D) negative women following sensitising events during the first trimester of pregnancy. The only exception is in multiple pregnancies where the standard 625 IU dose continues to be recommended. The 625 IU dose continues to be recommended for events occurring later in pregnancy.

During March 2008 NZBS will introduce a 250 IU mini-dose presentation of Rh(D) Immunoglobulin in New Zealand. The new presentation will be available on request from all NZBS and DHB Blood Banks. When Rh(D) Immunoglobulin is requested for a patient it will be important to ensure that the correct dose size is stated (one vial will no longer be adequate). NZBS has instructed Blood Banks to provide the 625 IU preparation when no dose size is stated. This instruction will be reviewed 2-3 months following implementation.

Currently approximately 9000 vials of the standard 625 IU dose size are issued each year in New Zealand. Data from Australia suggests that up to one third of these might be replaced by the new 250 IU presentation. If correct, this suggests that the introduction of the new presentation might reduce costs to the health sector by $250K. NZBS will closely monitor uptake of the new presentation to ensure that potential cost savings are realised by the DHBs.

Discussions are also taking place between the Ministry of Health, DHBs, RANZCOG, the New Zealand College of Midwives and NZBS in relation to the possible introduction of routine antenatal prophylaxis. International data indicates that this can further reduce the risk of allo-immunisation and consequent haemolytic disease of the newborn. Supplies of Anti-D Immunoglobulin are not a barrier to implementation. There are however a number of logistical issues that need to be addressed to ensure equity of access to all Rh(D) negative women. Routine antenatal prophylaxis also creates significant issues for blood banks and community laboratories involved in the screening of samples from pregnant women for allo-antibodies. These would need to be addressed as part of a co-ordinated plan for implementation.

Progesa Upgrade – Where Next?

In December 2007 NZBS attempted to implement an upgrade to the Progesa Blood Management system. This computer system is used by all NZBS sites and DHB managed blood banks. The implementation of the upgrade was unsuccessful and NZBS proceeded to restore the original version of Progesa. NZBS recognises the issues that this caused to the sector and apologises for any problems or inconvenience that it caused.

The current version of Progesa was initially introduced in 1999. Over the last 8 years the system has functioned well. The upgrade involved changes to both the hardware and software. This aimed to improve the overall performance, resilience and speed of the system. Software changes in the new version would have improved management of both patient and donor data across sites and extend functionality in a number of areas. Most importantly MAK-System, the supplier of Progesa, had indicated that the system was becoming difficult to support. Change was, and is, necessary to ensure ongoing support of this critical application.

Extensive testing had taken place prior to the attempted upgrade. The initial transition and migration went reasonably well. The system ran well initially but as the load increased it became increasingly slow and unworkable. This occurred despite a very significant increase in overall capacity of the hardware.

The supplier of the Progesa system is MAK-System, a French company. They are the largest international supplier of dedicated software for the blood industry. Progesa 4.4g, the upgraded version, is used successfully in many countries. The cause of the problems that we experienced are not yet clear. It appears however that they most likely relate to lower-level software which manages the database. NZBS continues to work closely with MAK-System to investigate this.

NZBS is committed to proceeding with upgrade work on the system. Once further plans are in place, we will communicate them widely. Further changes will only be attempted when the reasons for the problems encountered in December are fully understood and solutions identified.

On a positive note, blood banks responded well to the problems that were encountered. Manual systems were efficiently implemented and utilised over a period of several days. This was a very positive feature during a difficult period.

2006 Haemovigilance Report

Haemovigilance has become an integral part of transfusion medicine. The NZBS has adopted the Council of Europe definition of Haemovigilance which is, "*the organised surveillance procedures related to serious adverse or unexpected reactions in donors, or recipients and the epidemiological follow up of donors*". Haemovigilance schemes provide an opportunity to examine the frequency and causes of adverse events and to assist health professionals to understand the risks associated with blood transfusions.

New Zealand Blood Service (NZBS) formally introduced its Haemovigilance scheme on 1st May 2005. The scheme is modelled on similar systems in the UK & Ireland. Participation is voluntary and data from 20 of the 21 DHBs has been included in this second report.

13 adverse event categories are defined with nationwide data collected using a dedicated form and follow-up system. Events are categorised as serious or non-serious. This second annual report has recently been published. This covers events for the calendar year of 2006.

420 events were reported to the National Haemovigilance Office during the year, involving 385 recipients. Almost half (47.6%) of patients involved in the reports were over 60 years of age whereas paediatric patients made up 16% of the events reported. This reflects the recipient age profile in New Zealand. Male and female recipients experienced similar reported frequency of adverse events.

The majority (n=376) of events involved a single component or product. The frequency of transfusion related events by component was established from data accumulated since the beginning of the Haemovigilance scheme in 2005: platelets were the components most likely to be associated with an adverse event at 1:149, with fresh frozen plasma at 1:280 and red blood cells at 1:401.

Febrile non-haemolytic transfusion reactions continue to be the most frequently reported event (45% of all reports). Allergic reactions were the next most common (35%).

The incidence of incorrect blood component transfused (IBCT) rose from 10 (3.7%) in 2005 to 22 (5%) in 2006. The increase probably reflects better reporting rather than an increase in such events. During follow-up of IBCT events, location of the event was recorded. This showed that the majority of reports in 2006 showed a failure early in the chain of events (prescribing, sampling and in the laboratory). This is different to the international trend whereby most errors occur at the final bedside check.

The number of TRALI reports stayed the same at 10 (2.3%) events. TRALI is characterised by acute respiratory distress and non-cardiogenic lung oedema during or within six hours of transfusion and which is not temporally related to another cause of acute lung injury (ALI). It is agreed internationally that TRALI is poorly recognised and under-reported. Considerable educational efforts to improve reporting in all countries are required.

Seven cases of Transfusion Associated Circulatory Overload (TACO); ten of Delayed Transfusion Reaction (DTR) and two Acute Haemolytic reactions both involving platelets. The overall pattern of events was similar to that seen in 2005.

The continuing success of the Haemovigilance scheme is dependent upon the support of all those individuals who are involved in the transfusion process, including doctors, nurses, laboratory workers and patients. The NZBS is very appreciative of the time and effort that these individuals have given to ensure that the scheme is successful.

Remember: Report all adverse events regardless of severity or frequency.

The report also contains information on infectious marker results in blood donors and the results of the NZBS bacterial monitoring programme.

The full report is available on the NZBS website www.nzblood.co.nz. Printed copies are available from haemovigilance@nzblood.co.nz

Changes to CSL Products

During 2006 CSL Bioplasma undertook a major review of the presentation and labelling of its blood product range. The changes aim to introduce new packaging cartons and labels with a simplified design. This will make it easier for healthcare professionals to read the information on the labels and to reduce dosage and picking errors.

The new packaging and labelling have recently been approved by Medsafe and will be progressively introduced as new product is manufactured during this year. Current product will of course be fully utilised. This means that the new labelling will be introduced at different times at different sites across the country. The products are unchanged. Where possible, NZBS will alert key users in advance of the change.

As part of the new presentation, CSL are also changing the colour of the caps used on the vials. All newly manufactured product will have red caps rather then the blue ones used previously. Again this change will be introduced progressively during 2008.