New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

New Zealand Blood Service was established in 1998 in order to develop a nationally consistent approach to the provision of blood and blood products in New Zealand. The initial focus of the service has been on creating an infrastructure for the collection, processing and testing of donated blood. Much has been achieved in these areas and a period of consolidation is now required to ensure that maximum benefit is gained from the introduction of new systems and technologies. At the same time the focus of the service must now change. An increasing emphasis on the clinical aspects of transfusion service provision is now required.

Haemovigilance systems have been developed in a number of countries. The purpose of these systems is to collect data on untoward events associated with transfusion. This is then used to facilitate improvement in transfusion practice. Public awareness and concern around blood relates mainly to the risk of transmission of infection. Data from Haemovigilance systems however clearly indicates that most morbidity and mortality associated with transfusion occurs as a consequence of errors in the administration of blood transfusion. A recent case of an ABO incompatible transfusion in a New Zealand hospital suggests that there is an ongoing need to review current systems and to ensure that staff involved in the administration of blood are aware of potential risks. Transfusion Resource Nurses can play an important role in this area. During this year NZBS aims to appoint a number of such nurses. Their role will involve education and audit in relation to transfusion. This initiative will be progressed in close co-operation with Hospital Transfusion Committees.

The Australasian Society of Blood Transfusion and the National Health and Medical Research Council (NHMRC) have recently issued Clinical Practice Guidelines on the appropriate Use of Blood and Blood Products. The guidance is in two parts. The first dealing with use of red cells, is now in final form. Formal consultation on the second phase, covering the use of other blood components, ended in June. Final recommendations will be published in the near future. Copies of the Guidelines can be obtained from the NHMRC Website (www.nhmrc.health.gov.au). Further information on this initiative will be provided in future editions of *Blood Issues*.

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Nucleic Acid Testing For Blood-Borne Viruses In Donated Blood

The availability of various nucleic acid amplification technologies (NAT) has made genomic screening for infectious agents, in particular viruses, in donated blood possible. NATs include ligase chain reaction (LCR), transcription-medicated amplification (TMA), nucleic acid sequence-based amplification (NASBA) and polymerase chain reaction (PCR). All of these methods have been successfully applied to amplify sequences that are specific to a clinically relevant microorganisms. NATs are not only inherently specific but also have the advantage that they are capable of detection of the organism with a sensitivity several magnitudes higher than traditional serological methods.

Various NATs have been applied to detect viruses such as hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV). During the last few years, commercially produced NAT systems have become available.

At present Blood Transfusion Services screen donated blood using enzyme immuno assays (EIA) for viral antigens or antibodies, these include hepatitis B virus surface antigen (HBsAg), anti-HIV, anti-HCV etc. A residual risk of post transfusion infection from HIV and hepatitis virus remains. This is primarily due to the failure of the tests to detect the period of viraemia that precedes the development of antibody during the initial phase of the infection or the 'window-period'.

The window-period is the period between onset of an infection and our ability to detect that infection. The window-period as measured by conventional method using EIA for antibodies can be reduced significantly by direct testing for viral genomic RNA using NAT. The efficacy of the NAT test will depend on the level of viral nucleic acid in the blood during the early stage of infection, the level of reduction in the window period and the incidence of the infection in the donor population. NAT testing has been shown to be effective for HIV and HCV infection. The position for HBV infection is less clear since the level of HBV DNA present in blood prior to detection of HBsAg is low and not easily detected by current minipool NAT systems.

Window periods estimated by currently available techniques are as follows:

Virus	Window period By EIA (days)	Window period By NAT (days)
HIV	22	11
HBV	59	34
HCV	82	23

New Zealand Blood Service will be introducing NAT testing of donated blood later this year. At this stage, in common with Australia and the US, testing will focus on HCV and HIV.

The impetus for NAT testing came from the European plasma fractionators whose regulations were changed to require HCV NAT screened plasma for fractionation. Though there is no doubt that the NAT will make blood for transfusion safer we do not yet know how many NAT reactive but seronegative (EIA negative) donations we will identify. Experience from other countries suggests that most probably we will identify one or two such cases of HCV every year.

Responsibilities in Implementing a Blood Management Computer System

Computer systems for Blood Banks and Transfusion Services have evolved from meeting the more traditional goals of improve data storage and retrieval, into sophisticated information management systems. Using new and improved systems, one can improve transfusion safety and compliance with internal operational procedures as well as with regulatory and accreditation requirements. These modern systems achieve more accurate tracking of blood utilization, and improve operational communication and effective management reporting. This will enable better handling of critical business information and help to support new ways of delivering cost effective quality health care.

The purchaser also needs to be confident that they have acquired a product that will support them on a day-to-day basis in a safe and controlled manner, while at the same time keeping up with the evolving environment. There are two main imperatives required from a blood management system:

- The ability to track donor/recipient link
- Ensure donor and patient confidentiality

The benefits of implementing a Blood Management computer system are, however, coupled with responsibility.

The rational approach to the implementation and validation of a "total operational system" will involve the transfusion service and each blood bank defining which characteristics of a computer system are necessary and appropriate for its own operation

Blood Bank computer systems have a significant and positive impact on the safety of donors and patients. Those most knowledgeable about the medical, scientific and delivery aspects of blood banking must be directly involved in the selection and implementation of the computer system. Some confusion over differing terminology between the transfusion staff and the information systems (IS) vendor may arise, the project will benefit if a glossary of terms is produced prior to the validation and implementation process.

Acceptance testing protocols, as well as an overall quality assurance programme for the implementation project need to be developed by both the IS vendor and the transfusion staff. In addition, an error tracking and resolution mechanism must be in place.

Upon acceptance of a new computer system, its use must be integrated into the daily workflow of the blood bank. This process includes:

1. Acquiring a thorough understanding of the system.
2. Establishing policies and writing procedures for its use.
3. Providing initial training for staff and a continuing training programme.
4. Putting in place an error tracking and resolution system.
5. Setting up a well defined user security system.

The first step in applying the system to an operation is gaining a clear understanding of what the system should do, how it does it, and what the limitations are. Not enough emphasis can be given to the importance of staff training.

A training needs analysis should be carried out, based on interviews with operational staff, to identify specific training requirements. Ideally a training programme should include:

- An overview of the entire system
- A discussion of application and function
- A review of user defined options
- An introduction to systems documentation

Systems documentation, user guide, and training manuals, are typically measured in metres of paper and therefore, it is unlikely that it will ever be read from cover to cover. User documentation should be written, where possible, in a manner that can be used for teaching purposes. System logic diagrams and entity relationship diagrams should be included in the documentation.

Realistically, despite how well organised and well presented training programs are, or how familiar one may be with the documentation it is unlikely that the system will be fully appreciated until it has been put to the test, a process which may take many months.

Integration of a computer system into an operation requires a review of existing policies and procedures, the selection of user defined options compatible with those procedures (along with changes to those procedures), and then revising procedures to include computer specific steps. A formal change management procedure must be put in place as part of the implementation programme.

Simply put, validation is a process of evaluating software and documenting that required criteria are met. Inherent in this definition, not so obvious though, is that the testing should also be done to show that the system does not do what it should not do. Documentation confirming that validation testing has been performed must be maintained.

Following the intense activity associated with implementing a computer system, it is a natural tendency to pay less attention to how the system is working. It is also essential that during this period, the integrity of the database be maintained.

It is likely, however, in a system as complex as Blood Bank software that there will be bugs that have not been detected. A robust procedure for ongoing onsite evaluation must be put in place incorporating regular interaction between transfusion operational staff and the information system staff. New Zealand Blood Service (NZBS) has a statutory responsibility for the implementation of systems to support a safe and effective blood delivery service within New Zealand.

In 1999 NZBS published the plans for an integrated national blood service, and one of the central platforms was the selection and implementation of an integrated National Blood Management System (BMS). The introduction of the Manufacturing System was completed in October 2000, and today all blood that is collected, tested, and processed in New Zealand, is managed through the MAK Progesa system.

In addition to the added safety aspects, a national BMS system has provided a number of benefits to the service:

- A national view of stock information is readily available on stocks of blood components and manufactured products including their location
- An opportunity to define and implement standard operating systems for compatibility testing and including the controlled progression towards electronic crossmatching
- Common approaches to blood bank dispensing

Experience has shown that a combination of well designed, implemented and validated computer software programmes, along with carefully developed standard operating procedures, add to the safety and efficiency of the blood supply, and ultimately, enhance patient welfare.

Directed Blood Donations: A Controversial Issue

In spite of assurances by blood services and experts in the field of blood transfusion concerning the safety of the blood supply, public fears of receiving blood have increased since the advent of AIDS in early eighties. The patients demand absolute guarantee about the quality of blood. They look and sometimes ask for alternatives such as autologous blood. If this is not feasible, patients and their relatives often seek out potential donors (DD) who in their mind be "safer": than the blood that the volunteers donate to the Blood Service. Unfortunately this quest for safety obscures some very important issues like scientific reality and confidentiality.

Directed donors are well known to and chosen by the patient or the patient's family to be the "safe blood donor" but unfortunately it gives rise to problems of confidentiality. Directed donors pressured into donating by the patient or patient's family sometime fail to disclose risk behaviour that would normally disqualify them from donating because their past life or life-style or health conditions may be an embarrassment to the direct donor or their family or friend. Several studies support this concern - the medical literature clearly shows that the frequency of microbiological markers is higher in the directed donor population than that identified in volunteer donors.

Donation from close family members increases the likelihood that the donor and the patient will share the same HLA type. This increases the risk of Transfusion Associated Graft versus Host Disease (TA-GVHD). This is a rare but often fatal complication of transfusion. The risk of TA-GVHD can be eliminated by irradiating the blood components, but access to facilities for irradiation is limited. Delay in irradiation might delay availability of blood components derived from directed donations and may adversely effect patient outcome.

Directed Donation Policy of New Zealand Blood Service

New Zealand Blood Service does not support the practice of directed donations. NZBS will discourage requests to provide this for patients on the basis that there is no evidence that such components lead to improved patient care nor that they reduce the risk of acquiring transfusion associated infections.

Though NZBS does not support use of directed donation as a safer alternative to voluntarily donated blood, it accepts on rare occasions that it may be necessary to meet a special clinical need, for example HPA 1A negative platelet from the mother to treat allo-immune neonatal thrombocytopoenia.

A Standard Cryoprecipitate Product

Cryoprecipitate provides a source of fibrinogen for clinical treatment. In practice the most common problems treated with this blood product are bleeding, or the risk of bleeding, due to low levels of fibrinogen in plasma. Fibrinogen is needed to provide fibrin which is the main constituent of blood clots. The NZ Blood Service is currently introducing a changed cryoprecipitate product. The new product is better standardised and has a more efficient manufacturing process than was previously available in most Centres.

In clinical practice, most cryoprecipitate is used to treat people who have had extensive trauma and are receiving extensive transfusion support. It is also given to some cardiac surgery patients in whom the cardiac bypass procedure has resulted in dilution of fibrinogen to a low level and bleeding is continuing. Occasionally it may be needed by patients who are not synthesising enough fibrinogen due to liver disease, or to treat bleeding in renal failure, or other rare problems. Bleeding caused by low levels of fibrinogen cannot be stopped by surgical techniques as it results in persistent oozing from small blood vessels. It is one of the causes of microvascular haemostatic failure. Correction of the fibrinogen deficiency is required for efficient management.

What is Cryoprecipitate?

Cryoprecipitate is made from plasma by concentrating and separating some of the plasma proteins using a freeze-thaw process. The process makes use of the fact that fibrinogen, and some other plasma proteins, are insoluble at cold temperatures close to 0°C. These proteins can be concentrated by relatively simple methods that involve freezing plasma followed by thawing under controlled conditions. In the past, this process has resulted in a yield of fibrinogen of only about 40-50% from the original plasma. The new cryoprecipitate product is made using a novel step that enhances the yield of fibrinogen to about 70% or higher.

New Manufacturing Process

The new method has been developed from an observation made by an Australian transfusion scientist several years ago. Further work has been carried out in Dunedin[1] and Auckland to characterise the process and establish a suitable manufacturing method. The process employs a conditioning step in which frozen plasma is held at a temperature of -3°C to -5°C for a period of 24 hours. During this phase the plasma is only semi-frozen. It appears that the cold-insoluble proteins begin to undergo precipitation between the crystals of ice. Subsequently, the plasma is thawed at 0-4°C and the precipitated proteins (the cryo-proteins) which include fibrinogen, von Willebrand factor, factor VIII, factor XIII and fibronectin, etc, are separated by centrifugation. The process is carried out in sealed plastic blood product bags to ensure sterility throughout the process. The final product is then refrozen and stored below -30°C until thawed for clinical use.

Source of Plasma for Cryoprecipitate

The plasma for the new product is obtained by plasmapheresis using automated plasma collection machines. The donors are selected to have higher average fibrinogen levels so that the new product has a higher fibrinogen content than has generally been available in the past. Collection of a plasmapheresis donation takes approximately 40 minutes and it has a volume of 650-700mL. The process enables donors to give plasma donations more frequently than whole blood donations and ensures that vital plasma products are available in adequate quantities. Using plasmapheresis donors in this way has an added benefit for the recipient of the product: the cryoprecipitate recipient is exposed to fewer donors than when plasma is obtained from whole blood donations, and reduces any potential risk from blood borne infections.

The Standard National Product

The standard national cryoprecipitate product has an average volume of 100mL/bag (range: 80-120mL) and an average fibrinogen content of 1.4grams. The fibrinogen content has a relatively wide range (0.75 – 2g/unit and occasionally higher) due to the very wide range of fibrinogen concentration in the plasma of normal blood donors.

The usual dose for an adult patient is 2 or 3 bags (units), depending on patient's blood volume and fibrinogen level. This dose should produce an increment in plasma fibrinogen of about 1 g/L.

Although the new product contains von Willebrand factor (vWF), factor VIII and factor XIII, cryoprecipitate is not normally used to treat bleeding due to deficiencies of these factors now as other virally inactivated products are available. Although the manufacturing process gives a better yield of fibrinogen, the yield of vWF and factor VIII is not enhanced by the new production method.

Transfusing Cryoprecipitate

Cryoprecipitate should always be transfused promptly after it has been thawed. A standard filtered IV infusion set is used, as for other blood products. It is recommended that transfusion should be completed within 4 hours of thawing in case the product is excessively cooled and re-precipitation of the protein occurs.

Cryoprecipitate should only be given after laboratory confirmation that a patient has a low fibrinogen level which is causing, or is likely to cause, significant bleeding. A fibrinogen assay should therefore always be part of the initial evaluation of a bleeding patient. In non-surgical patients, clinical benefit from giving fibrinogen is unlikely if the plasma level is above 0.5 g/L, unless other factors such as uraemia are present. Surgical patients who are bleeding will often respond well to cryoprecipitate when the fibrinogen is below 1.0g/L, and sometimes in the range 1-1.3 g/L, but not commonly at higher levels[2,3].

References:

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2. American Society of Anesthesiology, Task Force on Blood Component Therapy. Practice Guidelines for blood component therapy. Anesthesiology 1996;84:732-47
3. Blauhut B. Thrombosis Research 1999;95:(4 Suppl 1):S63-9

CSL Update

CSL Bioplasma is responsible for the fractionation of plasma collected from volunteer donors in New Zealand. CSL continue to upgrade the range of products that they can produce. Two recent initiatives are of note:

1. The presentation of the 50ml bottles of Intragam P and Albumex 4 has recently changed. These products are now provided in a smaller bottle. The manufacturing process was unchanged.
2. Medsafe has recently given approval for the introduction of HIV RNA testing of plasma start pools. This change is in line with international regulatory requirements. A final date for implementation of testing has not yet been established.

CSL are also considering the introduction of Parvovirus B19 DNA screening of plasma destined for fractionation. This initiative would aim to reduce the viral load of B19 in plasma start pools. Parvovirus B19 is a small non-enveloped virus that is relatively resistant to current viral inactivation strategies applied to fractionated plasma products. Reduction in the viral load of the start pool will increase confidence that the viral inactivation methods employed to avoid transmission of this agent will be more assured.