New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

The Health Amendment Act, 1998, and the accompanying Gazette notice, resulted in the establishment of NZBS identified key responsibilities for the service. The provision of safe and effective blood and blood products was high on the priority list. NZBS is required to monitor international developments relating to blood safety and to consider their appropriateness in the New Zealand context.

During 2001 NZBS completed implementation of both universal leucodepletion and nucleic acid testing for HIV and HCV. All blood components issued for clinical transfusion to patients in New Zealand will now benefit from these new safety initiatives.

Recent developments in North America have resulted in a requirement to review the appropriateness of extending precautionary measures to further reduce the risk, currently theoretical, that vCJD might be transmitted by blood and blood products. Information on this is provided in this issue of the newsletter. NZBS will be pleased to receive comments and thoughts on this topic.

In February 2002 NZBS commenced the final stage of consultation on the review of Tissue typing and Allied Services. Documents have been distributed to key stakeholders, including clinical and managerial staff within the DHB network. The review aims to define an infrastructure that will facilitate improved service delivery in the future. Copies of the consultation documents can be obtained from the National Office of NZBS.

The NZBS Clinical Compendium will undergo a major revision during this month. This will be managed through our document control system. Planning for the development of a clinical website is now well advanced. This will allow greater access to the contents of the compendium and sources of clinical information provided by NZBS.

Comments on this newsletter, including identification of items for future issues, are encouraged. These should be addressed to Dr Susanta Ghosh at the NZBS Waikato Centre, or alternatively by email to (susanta.ghosh@nzblood.co.nz)

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Pre-transfusion Testing for Red Blood Cell Components

The objective of pre-transfusion testing is to ensure that the transfused red blood cells (RBCs) do not haemolyse excessively and enough of the transfused cells survive in the circulation. Although there is no argument about the need of pre-transfusion testing, there are controversies about the best and most efficient way to do it. In most blood banks pre-transfusion testing involves determining the patient's ABO and the Rhesus (D) group and screening patient's sera for red cell alloantibodies; then performing a major cross-match (testing the patient's serum against donor's red cells) to detect any incompatibility. Pre-transfusion testing ensures ABO compatibility between the donor and the recipient and should detect most, if not all clinically significant red cell alloantibodies that will react with donor's red cells.

Pre-transfusion testing has changed over the years. In the early days many blood banks also tested donor's serum against patient's red cells (minor cross-match). This practice was abandoned in the 70's and was replaced with routine antibody screening. The methods of antibody screening have also evolved considerably over time. Over the last 20 years or so in pre-transfusion testing, the approach has also changed from 'do all' approach to a more selective approach. This has helped not only to reduce the cost, but also to provide blood in a shorter time frame by cutting the number of tests and thus the time required, in most instances.

Current Standard Pre-transfusion Testing

Clerical Checking

The importance of collecting and properly labelling samples for pre-transfusion testing cannot be overemphasized. It is essential for safe blood transfusion. All samples received at the blood bank are checked to make sure that the information on the sample labels and the request form are identical. The patient's transfusion history is also checked. Any discrepancies must be resolved before blood can be issued for transfusion.

Blood Grouping

ABO group and Rhesus (D) type must be determined. ABO grouping is determined by testing red cells with anti-A and anti-B and testing the serum with A cells and B cells. Rhesus (D) type is determined by testing with anti-D. These results are checked against any historical result for confirmation. If no historical result is available the test is repeated.

Antibody Detection

Patient's serum or plasma is tested against a panel of reagent red cells. These reagent cells between them carry the blood group antigens necessary to detect most clinically significant blood group antibodies. The test system varies from place to place but it is usually an indirect anti-globulin test or a variant of it.

Antibody screening tests cannot detect all clinically significant antibodies. Those antigens not represented in a reagent cell panel (low incidence antigens) and those poorly expressed are likely to be missed.

If the antibody-screening test is positive, further serological testing is required to identify the antibody(s). Once the specificity of the antibody(s) has been identified the donor units must be screened for corresponding antigen to select the antigen negative units.

Cross-matching

After antibody screening, a cross-match is performed. This involves testing the patient's serum against red cells from the donor. The cross-match technique varies from blood bank to blood bank but usually for patients who are screen negative for red cell alloantibodies, an abbreviated cross-match is done just by mixing patient's serum with saline suspended donor red cells. On the other hand, if the screen is positive for red cell alloantibodies or the patient has a positive history of clinically significant antibodies a more comprehensive cross-match using an indirect antiglobulin test is performed. The reason for this selective approach is that the chance of missing a clinically significant antibody, when a well selected cell panel is used for antibody screening is very small.

Group and Screen

It is not necessary to cross-match blood in advance for patients undergoing surgical procedures that usually do not require blood transfusion. However, for these patients, blood is tested for ABO, Rhesus (D) type and red cell alloantibodies and stored in the blood bank in case it is needed for cross matching. When grouped and screened serum is available at the blood bank, cross-matched blood can be made available at short notice.

Electronic Cross-matching

Computers have been used to replace the abbreviated cross-match in patients who are antibody screen negative. In these situations the computer prevents release of ABO incompatible blood for transfusion. When used it must meet certain conditions. The first blood group is carried out using two different reagents for the red cell groups. The antibody screen is performed using a well-selected panel and finally, the blood is issued using the computer. This procedure can be applied to 90% or more of all cross-matches.

Electronic cross matching has the potential to reduce outdating of blood and to reduce the cross-match time.

Conclusion

Though pre-transfusion testing remains an essential test and there is no question about the importance of clerical checks, ABO, Rhesus (D) typing and antibody screening, the cross-matching process is changing and there is an increasing trend toward abbreviating the process and the use of computers in the process.

Cytomegalovirus and Transfusion

Cytomegalovirus (CMV) is a herpesvirus belonging to the Herpetoviridiae family. Other members of the family include herpes simplex type 1 and 2, Epstein-Barr virus and varicella zoster virus. All these viruses are double-stranded DNA viruses that are cell associated. They all share a common characteristic - they can remain latent in tissues following an acute infection. Following an infection CMV can be isolated from many organs and tissues including blood. It has been isolated from both fresh and stored blood and there is incontrovertible evidence that CMV can be transmitted by transfusion.

Factors predisposing to infection

CMV was first recognized as an infectious complication of blood transfusion in the 1960's in patients undergoing cardiopulmonary bypass requiring large volumes of fresh blood. Recently CMV infection in this group has declined, most probably due to changes in transfusion practice. CMV infection is usually inconsequential in most patients, but there is a group of patients for whom it remains an important cause of morbidity and mortality. These patients are immunocompromised and include premature infants, patients with immune dysfunction and patients whose immune response is impaired by immunosuppressive therapy. CMV infection in these patients can be associated with pneumonitis, hepatitis, retinitis, gastroenteritis and disseminated disease. Congenital CMV infection resulting from primary or reactivated infection in the mother can cause intrauterine or neonatal death or subsequent neurosensory impairment in infants.

Transmissibility of CMV varies from blood component to blood component. The two important factors that influence this variability include the number of white cells containing CMV virus in the component and the presence or absence of immune CMV antibody in the component. Transmissibility also varies amongst different groups of immunosuppressed patients depending on their CMV immune status and on the extent of the dysfunction of their cellular immunity. The risk has been defined in some groups but for some other groups it is yet to be established. Our current understanding of the indications for CMV safer products is identified below.

*Patients at Risk for Transfusion-Transmitted CMV Infection**

Patients for whom the risk is well established:

- CMV-seronegative pregnant women
- Premature infants (less than 1200g) born to CMV-seronegative women
- CMV-seronegative recipients of allogeneic bone-marrow transplant from CMV-seronegative donors
- CMV-seronegative patients with AIDS

Patients for whom the risk is less well established but sufficient to merit consideration:

- CMV-seronegative patients receiving organ transplants from CMV-seronegative donors
- CMV-seronegative patients who are potential candidates for bone-marrow transplant
- CMV-seronegative autologous bone-marrow transplant recipients
- CMV-seronegative patients undergoing splenectomy
- CMV-seronegative recipients of bone-marrow from
- CMV-seropositive donors

Patients for whom the risk is not established:

- CMV-seropositive recipients of bone-marrow transplant
- Full-term neonates
- CMV-seropositive recipients of solid organ allografts

*Adopted from: Sayers MH, Anderson KC et al. Ann Intern Med 1992;116:55

Prevention:

CMV-safer blood components should be used if a patient is at risk for transfusion-transmitted CMV infection. Blood obtained from CMV-seronegative donors is considered by many as standard CMV-safe blood. Because of limited availability of CMV-seronegative red cells and platelets, other approaches to reduce the risk of transfusion transmitted CMV have been investigated. As CMV is carried in white blood cells, leucodepletion of blood components has been investigated and leucodepleted blood components, produced by using recently developed highly efficient leucodepletion filters, has become an accepted method for prevention of transfusion transmitted CMV infection.

During 2001 the Canadian Blood Service undertook a Consensus Conference to address the issue of leucodepletion and CMV antibody testing. In particular the Conference assessed whether leucodepletion would remove the requirement for CMV antibody testing. The panel concluded that leucodepletion, using validated prestorage systems, was equivalent to CMV antibody testing in this regard. The panel however concluded, by a split recommendation, that in the absence of evidence that the two approaches were not additive, that CMV antibody screening should continue. The recommendations from the consensus have been published in Transfusion (2001 vol 41: 4: 560-69) and the proceeding of the conference is published in Transfusion Medicine reviews (2001: vol 15: 1:1-20).

NHMRC / ASBT Guideline on the Appropriate use of Red Blood Cells

Red cell transfusions are an integral part of management for many clinical conditions. Transfusion is used to increase oxygen carrying capacity of the blood by increasing the haemoglobin concentration of patients with acute or chronic anaemia. Though red cell transfusions have been in routine use for about hundred years now, there is little agreement on the precise indications for its use.

There are substantial differences in the clinical use of Red cell transfusions across New Zealand and Australia as well as overseas. These differences do not correlate with the clinical condition of the patients and can be found for the same procedure or diagnosis. This indicates that it depends on the individual clinician ordering the transfusion and also suggests that the inappropriate use of Red cell transfusion is a common occurrence.

Several factors have renewed the drive toward the most appropriate use of Red cell transfusions.

- Usage is not necessarily based on current scientific evidence and may not result in the best outcome for patients.
- There is renewed concern about the safety of transfusion, in relation to both infective and non-infective complications.
- There is increased pressure on the blood supply due to new safety requirements, such as donor deferral, leucodepletion and nucleic acid testing.

To address these issues, the development of a National Guideline on the appropriate use of Red cell components for New Zealand and Australia was initiated. In October 2001 National Health and Medical Research Council (NHMRC) and Australasian Society of Blood Transfusion (ASBT) in cooperation with the Royal Australasian College of Surgeons, the Australian and New Zealand College of Anaesthetists and other relevant groups have published Clinical Practice Guidelines on the use of Blood Components including that of red blood cells. The recommendations in the guideline aim to support:

- Clinical decisions about the use of red cells.
- Quality processes to promote appropriate uses of red cells and to optimize patient outcome.

A copy of the full document is available from the NHMRC Website at: http://www.nhmrc.gov.au or by contacting your local Transfusion Medicine Specialist. The summary of the guideline recommendations are as follows:

- Red blood cell transfusions should only be given when expected benefits to the patient are likely to outweigh the potential hazard.

- The patient's haemoglobin level, although important, should not be the sole deciding factor. Patient factors including signs and symptoms of hypoxia, ongoing blood loss, the risk to the patient of anaemia and risk of transfusion should be considered.
- The use of Red blood cells is likely to be inappropriate when the Hb is >100g/L unless there are specific indications. Reasons should be well documented if Red blood cells are given at this haemoglobin level.
- Use of Red blood cells is likely to be appropriate when the Hb is in the range of 70-100g/L. In such cases, the decision to transfuse should be supported by the need to relieve clinical signs and symptoms and to prevent significant morbidity and mortality.
- Use of Red blood cells is likely to be appropriate when the Hb is <70g/L. In some patients who are asymptomatic and/or where specific therapy is available, a lower threshold may be acceptable.

vCJD, Europe and Transfusion

There is currently no evidence that vCJD has been transmitted by transfusion of either blood components or fractionated blood products. The limited scientific data that is available however raises the possibility that this might occur. There is currently no screening test available for screening blood donations.

By January 2002, 109 deaths from vCJD had been reported in the UK. A further 4 cases have been described in France, 1 in Ireland, 1 in Hong Kong and most recently a suspected case in Italy (positive tonsillar biopsy). The cases from Ireland and Hong Kong had close links to the UK. This is not apparent in the French and Italian cases.

The first cases of BSE developed in the early 1980s. Analysis of the epidemic suggests a start point for the cattle epidemic in 1980. Between 1980 and 1996 the UK exported large amounts of cattle, beef and blood products to Europe and beyond. Manufacture and export of blood and bone meal continued during this period.

In 1989 the UK introduced strict precautions to reduce the risk that BSE might enter the human food chain (Specified bovine offal regulations, the SBO ban). In 1996, when the initial cases of vCJD were reported, a review identified poor compliance of the SBO ban. In the face of considerable public concern immediate steps were taken to rigidly enforce and monitor compliance with these requirements. European countries were slower to respond and evidence of compliance with these requirements, now an EU requirement, is limited.

The number of reported cases of BSE in the UK continues to decline. In contrast cases of BSE are increasing in a number of European countries. The total number of cases reported in Europe is however still small when compared with the size of the UK epidemic. Whilst the number of cases of BSE in the UK is falling a significant number of cases continue to be reported. Cases of BSE have also been reported in Japan during 2001.

Consideration of the requirement for precautionary measures to reduce the possibility that this disease might be transmissible by blood and blood products raises a number of complex issues. NZBS has taken a proactive approach in this area.

In February 2000 a UK donor deferral was implemented, this following identification of similar initiatives in the US and Canada. Since then many countries, including Australia, have introduced the same requirement. This deferral resulted in the exclusion of individuals who have spent a cumulative period of greater than 6 months in the UK between 1980 and 1996. 10 per cent of New Zealand donors were excluded as a consequence of this. During 2001 NZBS completed implementation of universal leucodepletion to further reduce the risk of transmission of this agent.

Evidence of increasing numbers of cases of BSE in European countries and recognition that food chain controls might not have been effectively introduced has resulted in consideration of extending current precautionary measures to include deferral based on residency in Europe. Divergent approaches have developed in North America. Health Canada introduced new measures in September 2001 shortly followed by the American Red Cross in November of last year.

In January this year the US FDA published final guidance relating to precautionary measures to reduce the risk that CJD and vCJD might be transmitted by transfusion of blood and blood products. Copies of the FDA Guidance can be obtained from the FDA Website **(www.fda.gov/cber/gdlns/cjdvcjd)**

New Zealand Blood Service has been monitoring the situation carefully and has undertaken further donor travel surveys to evaluate the impact that introduction of such measures might have if they were introduced in New Zealand.

The key measures identified in the new FDA Guidance are:

- A reduction in the period of residency in the UK that results in deferral from 6 to 3 months
- Deferral of prospective donors who have been resident in European countries, other than the UK, for a cumulative period of 5 years from 1980
- Permanent exclusion of prospective donors who have received a blood transfusion in the UK since 1980.

Introduction of a similar package of measures in New Zealand would result in the exclusion of a further 2% of donors. The majority of these, 1.8%, relate to the change in the UK donor exclusion from 6 to 3 months.

NZBS plans to hold a consultation with stakeholders on this issue to determine what further precautionary measures, if any, should be taken in New Zealand to further reduce the theoretical risk of transmission of vCJD by transfusion.