New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

During July NZBS will launch its new Transfusion Medicine Handbook. This book, designed as a pocket sized ready reference, will be made available free of charge to all health professionals involved in the delivery of blood products to patients.

The approach adopted in compiling this handbook has been to survey similar publications prepared by blood transfusion services in other countries as well as placing special emphasis on literature relating to blood transfusion of published consensus guidelines. Another important source is the publications of regulatory bodies such as the guide prepared by the Council of Europe which provides the basis for essential requirements for the manufacture of blood components and blood products that govern practices in New Zealand.

The handbook is not a textbook for transfusion medicine or a compendium for product specifications. It is a guide to the essential information and requirements that will assist clinical and blood bank staff in making appropriate choices for the prescription of blood components and blood products for the treatment of patients. It outlines procedures for the safe administration of these components and products and it is designed to highlight issues of risk that are associated with the use of biological therapeutic materials. It encourages consultation with appropriate specialists in situations of clinical complexity, clinical vigilance and the importance of recording and reporting adverse events. When read in association with hospital operating policies and procedures, these measures, when appropriately implemented can do much to improve the effectiveness and safety of blood transfusion products in the treatment of patients.

In addition to the printed version the contents of the handbook can be accessed in pdf format from the New Zealand Blood Service Internet Site which readers are encouraged to visit (www.nzblood.co.nz). The website provides links to a number of Web Sites mentioned in the handbook

Comment on the presentation and content of this booklet directed to the New Zealand Blood Service is encouraged and will be most appreciated to assist improvements to the regular updates that will be necessary in the years ahead.

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Neonatal Alloimmune Thrombocytopenia

Neonatal Alloimmune Thrombocytopenia (NAIT) is the most frequent clinical problem arising from immunisation against platelet specific alloantigens. This condition is believed to affect around 1 in 2000 live births. It arises from maternal immunisation against foetal platelet antigens. In Caucasian women, anti-HPA-1a antibody is implicated in 80-90% of cases and anti-HPA-5b antibody accounts for a further 5-15%. It has been considered the platelet counterpart of Rh haemolytic disease of the newborn, but in contrast to this condition, NAIT affects the first-born in 40-60% of cases. Subsequent pregnancies are affected in 75-90% of cases.

The major risk is intracranial haemorrhage in those with severe thrombocytopenia and may lead to death in 10% or neurological sequelae in 20% of cases. However, there is a broad spectrum of clinical presentation and the unexpected first case may be symptomless and only discovered incidentally following a full blood count. The presence of a purpuric rash should alert one to the possibility of NAIT.

The diagnosis of NAIT is initially made on clinical grounds and requires exclusion of other causes of neonatal thrombocytopenia such as infection, disseminated intravascular coagulation, and maternal immune thrombocytopenia purpura (ITP). Early discussion with a Transfusion Medicine Specialist is recommended both for diagnostic reasons and for the subsequent supply of patient-specific platelet units.

The platelet count can continue to fall during the first 48 hours after birth and should be monitored daily. An ultrasound scan for possible intracranial haemorrhage should be performed if there is significant thrombocytopenia

Laboratory confirmation of the diagnosis is required. In NZBS Auckland, a Solid Phase Red Cell Adherence (SPRCA) test is first performed. This tests the mother's serum against the father's platelets (which is a good source of the platelet antigen involved). If this test is positive then both parents' samples are analysed by PCR looking at the platelet antigen genes. In addition, the maternal specimen is tested against a panel of platelets of known phenotype to determine the antibody's specificity and to confirm that the antibody is directed at platelet-specific antigens rather than HLA antigens.

For antibodies directed against certain platelet antigens, the SPRCA technique may be unable to detect their presence. In this situation the more sensitive Monoclonal Antibody-Specific Immobilisation of Platelet Antigens (MAIPA) technique is utilised.

Late in pregnancy the level of the anti-platelet antibody may drop and become undetectable. When the initial SPRCA crossmatch test is negative then a repeat maternal specimen six weeks later is recommended.

If there is a risk of bleeding then a compatible platelet transfusion should be given. In Auckland, there is a small panel of potential platelet donors who are HPA-1a negative. The platelet donors on our panel deserve our admiration and gratitude. They often tolerate significant interruption to their daily lives since they are asked to donate at very short notice. There is no doubt that their contribution has resulted in prevention of intracranial haemorrhage and possibly death.

An alternative to specially selected donor platelets is to transfuse maternal platelets to the neonate. The special requirements for maternal platelets include the washing of these platelets to remove maternal plasma (which contains the implicated antibody) and the irradiation of the collected platelets to reduce the risk of transfusion-associated graft versus host disease (a rare but usually fatal complication).

Whatever the source of the platelets, it is useful to perform a platelet count 30-60 minutes after the transfusion to confirm a beneficial increment.

If platelets are not available, high dose IV immunoglobulin (1 g/kg/day for 1-3 days) may be used. When IV immunoglobulin is used the effect on the platelet count is delayed for 24-48 hours though it can be effective in up to 75% of cases.

Transfusion Related Acute Lung Injury (TRALI)

Clinical Features

TRALI is a syndrome characterised by acute respiratory distress. It was first described in 1951. Clinical features of TRALI include bilateral pulmonary oedema, arterial hypoxaemia, tachycardia, fever, hypotension and cyanosis. The symptoms usually arise within 1-2 hours of transfusion of plasma containing blood components and always within 1-6 hours. Patients with TRALI have normal CVP and normal/low pulmonary wedge pressure. Approximately 80% of patients with TRALI improve within 48-96 hours, provided there is prompt and vigorous respiratory support.[1] The pulmonary lesion is typically transient, with return of pO_2 to pretransfusion levels and no evidence of permanent sequelae.[2] Mortality rate appears to be 5-13%[1]. There is no diagnostic test and TRALI is usually a diagnosis of exclusion.

Incidence

The true incidence of TRALI is unknown. One study from the 1980s reported an incidence of 1 in 5000 plasma-containing transfusions was associated with this reaction.[1] In New Zealand an incidence of 0.001% was reported from a total of 440,000 blood components transfused between 1981 and 1987.[3] The 20 fold difference in incidence may reflect variable levels of awareness and reporting. TRALI is felt to be significantly underdiagnosed. There does not appear to be a preponderance of sex, age or disease associations in patients with TRALI.

Differential Diagnosis

DIFFERENTIAL DIAGNOSIS	DISTINGUISHING FEATURES
Anaphylactic transfusion reaction	▪ Bronchospasm and laryngeal oedema predominate ▪ Erythema, urticaria ▪ Fever not a manifestation
Circulatory overload	▪ Hypertension, tachycardia ▪ Elevated CVP ▪ Onset within hours of any type of blood component
Bacterial contamination	▪ Fever, hypotension vascular collapse are prominent symptoms

Implicated Blood Components

These include whole blood, red blood cells, granulocytes collected by apheresis, platelets and cryoprecipitate. In most instances the blood component contains more than 60mL of plasma.

Fractionated plasma products such as albumin and immunoglobulin that are manufactured from large pools of plasma donors have not been associated with any case reports.[1]

Pathogenesis of TRALI

TRALI is assumed to be an immune-mediated event. Typically the pathologic antibodies are of donor origin. Reports have documented the presence of HLA Class I and Class II antibodies as well as neutrophil specific antibodies (anti-NA2, anti-5b and anti-NB2) in the serum of implicated units.

HLA specific antibodies or leukoagglutinins in donor plasma were found in 89% of 36 cases.[2]

An analysis of 46 cases reported to the American Red Cross from 1990 to 1998 identified cases with granulocyte-specific antibodies (41%) were more common than those with HLA antibodies (28%).[4]

These antibodies are usually found in the blood of multiparous donors.

Passive transfer of leucocyte antibodies from donor plasma reacts with the recipient's circulating and marginated pool of leucocytes. This leads to complement activation (C5a), neutrophil aggregation, margination and sequestration in pulmonary microvasculature, release of proteases, oxygen radicals and acidic lipids from neutrophils, which damages pulmonary vascular endothelium, with subsequent extra vasation of protein-laden fluid into the interstitium and alveoli.

Autopsy of a patient who died of TRALI demonstrated pulmonary oedema with granulocyte aggregation within the pulmonary microvasculature. Electron microscopy revealed capillary endothelial damage with activated granulocytes in contact with alveolar basement membranes.

Although there is data to suggest that the implicated antibody is specific for a recipient epitope, there are cases of TRALI that are left unexplained where HLA or neutrophil-specific antibody does not share epitopes with the recipient.[1] In 5-15% of cases, no antibody has been identified in either the patient or donor.[1]

A non antibody-mediated model of TRALI postulates that a neutrophil priming agent – a lipid, develops during storage of blood components and that it primes polymorphonuclear oxidase. The investigators described the presence of this lipid in a cohort of TRALI patients in whom no HLA or leucocyte antibodies were found.[5]

Another mechanism involves cytokines (e.g. TNF-$\propto$) which are also implicated in haemolytic transfusion reactions.

Management of TRALI

Respiratory support should be as intensive as dictated by the clinical picture. In one of the largest studies of TRALI 100% of 36 patients required oxygen support, while 72% required short-term mechanical ventilation.[2]

Vasopresser agents may be useful in cases of persistent hypotension. Corticosteroids are probably of marginal value and diuretics have no role because of the underlying pathology involves microvascular injury, rather than fluid overload.[1]

The majority of cases do not require special measures to manage future transfusions. In New Zealand all components are leucodepleted at the point of manufacture, theoretically reducing the risk in recipients where an antibody has been identified.

Recommendations have been made to permanently defer donors who have been implicated in TRALI, unless subsequent donations are limited to the production of washed red blood cells.

Screening of multiparous donors for HLA and granulocyte antibodies is not practical for a number of reasons:

- The donor history may not identify alloimmunising events such as ectopic pregnancy or abortion
- It fails to recognise donors who have been immunised by transfusion
- Tests for HLA and granulocyte antibodies are time consuming and not routinely available in many blood centres
- Deferring blood component production from multiparous women would result in a significant loss of blood donors

Development of strategies to prevent TRALI are complicated by the absence of a profile of recipients at risk and the lack of a diagnostic test.

It is important that all suspected cases of TRALI are reported and investigated.

References

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Haemophilia Workshop

A joint DHBNZ/DHBs and NZBS workshop is to be held during June to discuss a number of issues relating to the availability of products used in the management of Haemophilia.

The goals of the workshop will be:

1. A shared understanding of the current issues relating to management of demand for haemophilia products, in particular Factor VIII.
2. A national perspective on the appropriateness of introduction of Biostate in New Zealand.
3. The definition of an optimal mix of plasma derived versus recombinant Factor VIII for Haemophilia management in New Zealand and identification of interventions that might support this being achieved.
4. Consideration of the benefits of a national co-ordination, procurement and management of products used in the management of Haemophilia.

A background to the issues is provided below.

Haemophilia A is a sex linked genetic disorder that results in low levels of circulating Factor VIII. The clinical manifestations of the disorder are largely related to the level of Factor VIII. In severe cases Factor VIII replacement therapy will be required for management of spontaneous bleeds. In less severe cases replacement therapy may only be required for operative and similar interventions.

Factor VIII concentrates are a relatively recent development in modern medicine and these have been widely available only for the last 40 years. The availability of Factor VIII concentrates has dramatically altered the lives of people with haemophilia. Prior to the easy availability of factor concentrates frequent joint bleeds led to progressive joint disease with associated disability. These problems are still evident in older haemophiliacs today. Factor concentrates have enabled more effective early intervention and treatment of bleeding episodes. Today people with haemophilia are able to lead near normal lives, with access to home treatment and prophylactic treatment programmes.

Unfortunately the improvement in quality of life has come at considerable cost for many people with

Haemophilia. Non virally treated factor concentrates manufactured from large plasma pools proved to be highly effective vectors of blood borne viral infections. Many haemophiliacs developed HIV and Hepatitis C infection during the 1980s.

Recognition of the potential for fractionated plasma products to transmit viral infection has impacted significantly on the blood industry during the last 20 years.

- The Haemophilia community has understandably become risk averse. Lobby groups have emerged with the aim of ensuring access to the highest standards of medical care.
- Regulatory authorities internationally have enforced rigorous standards on the plasma fractionation industry necessitating the introduction of validated specific viral inactivation technologies into the manufacture of factor concentrates.
- Litigation has occurred in many countries. France,Canada and the Republic of Ireland have been most severely affected. In France during the early 1990s prominent transfusion specialists were imprisoned following investigations into the introduction of HIV antibody testing and heat treatment of factor concentrates. In 2002 the Canadian Authorities commenced legal action against senior Canadian Red Cross and Industry figures. A series of tribunals in Ireland has impacted significantly on confidence in the blood supply.
- Recent concerns in relation to the potential that variant CJD might be transmitted by transfusion of blood and blood products has led to inevitable concern and the industry is currently attempting to address these concerns.
- Alternative therapeutic products for the management of Haemophilia A, in particular recombinant products have been developed and some current products can be manufactured without coming into contact with any plasma proteins. These are perceived by many to be superior to plasma derived products.

Factor concentrates available today have an enviable safety record with respect to viruses. The cost of achieving this has been high and this is reflected in the price of the products.

Two types of product are currently available for the management of patients with severe Haemophilia A. These comprise products derived from human plasma and recombinant products. Currently, approximately 62% of total Factor VIII used in New Zealand is derived from plasma and 38% is recombinant in nature.

Plasma derived products used in New Zealand are manufactured from plasma donated by New Zealand donors. The plasma is sent to CSL Bioplasma where it is currently used to produce AHF. This is an intermediate purity product that has been available for many years.

AHF has an excellent safety record with regard to viral transmission and there are no reports of HIV or HCV transmission by AHF. The product is identical to 8Y manufactured by BPL for distribution in England. Its manufacture includes a terminal dry heat step of proven efficacy and AHF is the only plasma derived Factor VIII concentrate currently available in New Zealand.

More recently CSL Bioplasma have developed a new product, Biostate which is a high purity product that has been formulated to contain significant levels of both Factor VIIIc and also Factor VIII vWF. In Australia the TGA has mandated the introduction of Biostate effective from April 2003 and AHF was removed from the Therapeutics Goods Register at the same time. The decision to mandate Biostate as a replacement for AHF was made on safety grounds. Biostate has two specific viral inactivation steps whereas AHF has only one. Preliminary data suggests that clearance of the prion, the infectious agent of vCJD, will be significantly higher in Biostate than for AHF. A position on Biostate in New Zealand has not yet been established.

Recombinant products are currently restricted to newly diagnosed, or virgin Haemophiliacs, and to haemophiliacs less than 18 years old who do not have evidence of infection with either HIV or HCV. In practice however, as Haemophiliacs become older they continue to be maintained on recombinant products.

Three recombinant products are currently available, Kogenate manufactured by Bayer, Recombinate manufactured by Baxter and a product manufactured by Wyeth. During 2001 severe shortages of recombinant Factor VIII were experienced world-wide as a consequence of problems in the Bayer manufacturing facilities. Recombinant factor procurement is currently managed on a site by site basis by individual DHBs.

Severe hypotensive reactions following Platelet Transfusions Medical Alert Update

A Medical Alert was issued on 31 January 2003 reporting that four hypotensive reactions had occurred involving adult patients who had undergone surgery involving cardiopulmonary bypass. These patients had been transfused with pooled platelet preparations. As a precautionary measure NZBS issued an instruction to Blood Banks that apheresis platelet preparations should be provided for perioperative transfusion support of cardiac surgery patients.

NZBS initiated an investigation into the cluster of cases and the findings of this investigation have been reported. The review failed to identify an obvious explanation for the reactions and it is noteworthy that in the period following issue of the alert no further cases have been identified. During this period only apheresis platelet preparations have been used.

On 6 May 2003 the NZBS Clinical Advisory Group reviewed the data and recommended that the requirement to utilise only apheresis platelets in patients undergoing cardiac surgery should be removed, that close monitoring should continue and that the situation reassessed should any new reactions emerge. Adverse reactions should continue to be reported to your local Blood Bank using the established reporting system.