# BLOOD ISSUES

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## NZBS TO IMPLEMENT MEASURES TO IMPROVE SAFETY AND MORE EFFECTIVE UTILISATION OF PLATELET COMPONENTS

In March this year NZBS received approval from Medsafe to introduce a range of changes to the current specifications of platelet components. This will include implementation of a comprehensive bacterial screening programme and an extension of the shelf life to 7 days. Plans are now being progressed to support implementation in Auckland around July this year with a subsequent rollout across the country.

The systems that will be implemented by NZBS are identical to those used by the National Blood Service in England (NHSBT) where considerable data has been accumulated to demonstrate that the approach is safe and does not adversely impact on the clinical efficacy of the components.

This edition of Blood Issues provides information on the risks of bacterial contamination of platelets and the likely clinical impact of the extended shelf-life of the components.

### Bacterial Contamination of Platelet Components

Platelet components are routinely stored at 20-24 degrees Celsius. This temperature supports growth of bacteria more efficiently than the refrigerated storage of red cell components. The Council of Europe Guide identifies that bacterial contamination can occur in 0.2 to 0.4% of platelet components.

Most instances of bacterial contamination occur at the time of blood donation. This arises because of inadequate skin preparation of the phlebotomy site or the presence of a small core of skin entering the collection pack through the large bore needle. This normally results in low levels of gram positive bacteria such as staphylococcus epidermidis or less commonly staphylococcus aureus. This type of contamination can be reduced by well validated skin disinfection systems combined with the diversion of the first 30-40mLs of the donation in order to avoid skin commensals contaminating the donation. These measures can reduce the frequency of bacterial contamination in platelet components by approximately 60-70%. Less common causes of contamination include low level occult bacteraemia in the donor and breaches of the closed system blood collection pack.

NZBS implemented a programme to monitor the frequency of bacterial contamination of platelet components during 2004. The proportion of components screened has increased progressively and is currently just over 90%. The monitoring system involves a 7mL sample being inoculated into an aerobic blood culture bottle which is subsequently cultured using a Bac-T-Alert system (the same system used for routine blood culture in many hospitals). Data from this programme compares well with international data with reactive culture results seen in 0.11% of tested components and confirmed positive cultures in 0.02%.

### Bacterial Sepsis and Platelet Transfusion

The frequency of clinical complications associated with bacterial contamination is much lower than might be anticipated from the results of routine screening. Nonetheless serious problems can occur and there are reports of serious morbidity and mortality in the international literature.

Four cases of bacterial sepsis associated with platelet transfusion have been reported to the NZBS Haemovigilance Office in the period 2007-2014.

Two of the reports were assessed as high imputability (transfusion considered to be the likely source). In both cases the platelet component responsible for the reaction had not been sampled as part of the routine bacterial monitoring programme. The reactions were not considered severe and the patients recovered following administration of appropriate antibiotics.

The imputability of the remaining two reports was assessed as possible (when the evidence is clearly indeterminate for attributing the event either to the transfusion or alternative causes). Both cases involved patients who were severely pancytopenic following treatment for Acute Myeloid Leukaemia. One reaction was considered most likely due to an infected central line and the other most likely to the contamination of the component due to handling errors following the reaction. Neither reaction was considered severe and both patients recovered fully. The platelet component implicated in these two events had been tested on day 2 prior to release with negative results.

During early 2015 a further case of sepsis has occurred. This involved a platelet component that had been included in the monitoring programme. The recipient developed a high fever with rigors during the transfusion. A gram stain on the platelet component showed the presence of gram positive cocci and culture grew Staph aureus. The patient responded well to treatment with antibiotics and made a full recovery.

### Proposed Bacterial Testing System

The system that NZBS will be implementing is more sensitive than the one used in the current monitoring programme. The key changes involve an increase in the volume of the inoculum to a minimum of 7.5mL (up to 10mL) and the use of a two bottle system (aerobic and anaerobic bottles) as opposed to the single aerobic bottle currently in use.

The increase in total sample volume from 6mL to 20mL (minimum 15mL) is particularly important. International

experience indicates that the frequency of reactive results increases with the volume of sample. This reflects the effect of the Poisson sampling effect. Bacteria in platelets function as particles and at low levels of contamination, as occurs in healthy donors, the likelihood of the sample including bacteria will increase with the volume of the sample.

The anaerobic bottle will allow detection of anaerobic bacteria such as Propionibacterium acnes. More importantly it also detects many aerobic bacteria and hence improves overall system sensitivity.

## Clinical Impact of Extending the Platelet Shelf Life

A number of countries, mainly in Europe, utilise a 7 day shelf life for platelet components. This includes the Netherlands, Denmark and England. No clinical concerns have arisen that have been attributed to this.

A recent study co-ordinated by the English National Blood Service (NHSBT) compared the clinical efficacy of platelets stored for 2-5 days versus 6-7 days in preventing and treating haemorrhage in patients with thrombocytopenia. It was a non-inferiority trial with randomised block, cross-over design. The study demonstrated that 6-7 day platelets demonstrated equivalent clinical efficacy when compared with 2-5 day platelets. In particular there was no difference in bleeding score between the two groups, no difference in inter-transfusion interval and no difference in the incidence of adverse events or transfusion reactions.

The NHSBT study was performed using platelets suspended in plasma. NZBS uses a platelet additive solution. This reduces the frequency and severity of febrile and allergic transfusion reactions and also maximises the availability of plasma for fractionation.

There is considerable in-vitro data to demonstrate that platelets in additive solution continue to function well for up to 9 days. This has been confirmed by in-vivo studies that have shown acceptable platelet increments and platelet recovery out to day 8.

## Logistical Benefits of Extended Shelf Life

The current short shelf life of platelet components is associated with high expiry rates of between 20-30%. This in part reflects the high variability in clinical demand for platelet components and also the geography of the country. Smaller DHBs that are distant from the main NZBS hub sites will maintain a small stock of platelets for use in emergency settings. Extension of the shelf life will reduce the number of components stored over the year and at the same time improve confidence in safety with respect of bacterial contamination.

The NHSBT study referred to earlier identified that extension of the shelf life beyond five days has significantly improved management of platelet stocks, both within Blood Centres and hospital blood banks and has been well received by hospital customers.

## Implementation Plans

Medsafe required NZBS to provide an overview of the planned implementation of the new systems and to identify specific proposals for post implementation monitoring. This includes provision of information to clinical users of the components and methods for targeted haemovigilance in the early implementation phase. This edition of Blood Issues begins this process.

The implementation of platelets with a seven day shelf life will be piloted at the Auckland Blood Centre. We anticipate that the pilot will last for a minimum period of three months and will only be extended to the other NZBS Centres once a formal review of the outcome of the pilot has been completed.

NZBS will provide advance warning to Hospital Transfusion Committees at each DHB prior to the introduction of the extended shelf life.

The clinical phase of the post implementation monitoring will comprise review of a minimum 50 platelet transfusion episodes involving transfusion of day 6 to 7 day platelets. Information will be collated on platelet increments, clinical response to the transfusion and the occurrence of adverse reactions.

NZBS used a similar approach to the introduction of platelets in additive solution in 2012 and will compare the clinical data on day 6 and 7 platelets to this earlier data on platelets transfused with a 5 day shelf life.

## Management of Suspected Transfusion Reactions

NZBS provides guidelines on the appropriate management and reporting of suspected transfusion reactions. These can be accessed on the NZBS website: (http://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/Guidelines-for-Management-of-Adverse-Transfusion-Reactions-111l015.pdf) or on the Blood Resource sites on local DHB intranets.

## PLANNED IMPLEMENTATION OF e-TRACELINE

NZBS has recently commenced planning for the implementation of an update to the computer system used to manage hospital blood bank activity. Hospital Blood Banks currently utilise the blood bank module of the e-Progesa system (the main NZBS blood management system). This approach works reasonably well. Implementation of e-Traceline will however provide additional functionality that will support improvements to the services provided. In particular e-Traceline will support the use of 'smart fridges' within hospitals. Smart fridges function as an extension of the red cell component inventory of the hospital blood bank. Red cell components can be allocated to individual patients and immediately accessed from the smart fridge. This type of approach will potentially streamline availability of red cell components in operating theatres and reduce the risk of delays due to transportation for those patients where a valid group and screen result is available. These systems will work particularly well for more remote clinical locations in the DHB and potentially also for private hospitals.

Initial work has commenced on the development of a business case for the project. It is anticipated that this will be completed by the end of the current financial year and allow work to begin on configuration and functional design in the second half of this year. Current plans identify the new system being implemented in either late 2016 or early 2017. Development of systems to support use of smart fridges will then begin. Realistically the earliest that a smart fridge will be available will be during 2018 and rollout to all interested sites across the country will likely take considerable time.

e-Traceline will provide a range of other opportunities and will in particular provide significant benefits for the teams working in hospital blood banks. The system will bring a capability to automate stock management within hospital blood banks and support automatic re-stocking to agreed designated levels. The system will also support visibility of information on pre-transfusion sample validity in DHB electronic record systems.

NZBS is considering a move to a single national patient database linked into the implementation of e-Traceline. This would improve visibility of patient results across DHBs and ensure that all transfusion information is easily visible wherever the patient presents in the country. Most importantly this would avoid duplication of patient records as can occur within the current e-Progesa system. A formal Privacy Impact Assessment will be undertaken before a final decision is made to progress this.

## PLANNED CHANGES TO PRESENTATION OF EVOGAM

Evogam is the subcutaneous product produced by CSL Behring Australia from New Zealand plasma. It is used mainly in the treatment of people with immunodeficiencies and allows self-administration of the immunoglobulin replacement therapy.

CSL Behring have received approval from Medsafe to introduce smaller vial sizes for the product. No changes are being made to either the product or the amount of immunoglobulin present in each vial.

The changes will be applied to Evogam produced from the plasma pool processed in March 2015. Product from this pool will be supplied to patients from June 2015. Clinicians and patients who use the product will be provided with more detailed information closer to the date of introduction.

More information on the changes can be obtained from the NZBS Transfusion Nurse Specialists. Contact details can be obtained via your local hospital blood bank.

## UPDATE TO CSL BEHRING Rh(D) IMMUNOGLOBULIN-VF DATASHEET

CSL Behring Australia have recently updated their datasheet on Rh(D) Immunoglobulin-VF. The key change is the introduction of a new precautionary statement concerning the use of this product in patients with a body mass index of ≥30. The datasheet identifies that there is an increased risk of lack of effect in such patients and recommends that the clearance of foetal cells and the presence of Rh(D) antibody should be confirmed post administration.

The updated datasheet can be accessed from the NZBS website (www.nzblood.co.nz) or from the DHB Blood Resource folder.

The CSL Behring product is suitable for intramuscular use only. NZBS provides an intravenous Rh(D) immunoglobulin for selected patients who have had a larger foeto-maternal bleed necessitating a larger dose of the product. Supplies of this product are limited and, at this stage, it should not be considered as an alternative to the standard intramuscular product for patients with a high BMI. Prior approval from an NZBS Medical Officer is required to access the intravenous product.

## AGE OF BLOOD AT TRANSFUSION – IS FRESH BEST?

A number of changes occur progressively in stored red cells. This includes metabolic changes, reduced deformability of the red cells and accumulation of a range of biologically active substances. A series of reports based on retrospective analysis of patient outcomes published during 2006 and 2008 raised the possibility that these changes might be associated with adverse clinical outcome. This led to questions as to whether fresher red cell components should be used when transfusing critically ill patients. This resulted in the development of a number of randomised controlled trials that aimed to provide a definitive answer to the question. One of these is the TRANSFUSE study which is co-ordinated by the ANZICS study group. A number of hospitals across New Zealand are involved in this.

The results of some of the randomised controlled studies are now starting to become available. The first, the ARIPI study, investigated the use of red cells that were stored for 7 days or less against standard red cells in premature neonates. The second, the ABLE study, evaluated red cells stored for 8 days or less against standard red cells in critically ill patients. The results of the RECESS study have also been presented at an international meeting. This evaluated the use of red cell components less than 10 days old versus standard issue in cardiac surgery patients. All three studies reported no benefit to the transfusion of fresh red cells.

These initial reports are reassuring but more data is still needed to confirm the conclusions and improve confidence in the use of older red cells.

NZBS has developed a 'Fresh Blood' policy to ensure a consistent approach to this issue across the sector. A copy is available on the NZBS website: (http://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/NZBS-Policy-on-Use-of-Fresh-Blood-111P074.pdf).

## IMPLEMENTATION OF REVISED BEHAVIOURAL DONOR DEFERRAL CRITERIA

During 2013 NZBS commissioned a further independent expert review of the behavioural donor deferral criteria. This review was initiated as part of NZBS' commitment to re-examine the criteria after a five year interval following the last changes made in 2009.

The expert group delivered its recommendations to NZBS in February 2014. These were accepted in full by

the NZBS Board, subsequently approved by Medsafe in September and implemented in December 2014. The main changes to the criteria are:

- The deferral period for men who have sex with men is changed to 12 months from five years following their last sexual encounter.
- The deferral period for former residents of countries considered to be high risk for HIV infection to be changed to 12 months from five years.
- The deferral period for sex workers after engaging in sex work (prostitution) in New Zealand or overseas is to be aligned at 12 months.

These changes will bring into line the approach used by NZBS to that currently in place in Australia and the United Kingdom.

A copy of the report of the expert group is available on the NZBS website:

http://www.nzblood.co.nz/news/2014/revised-donor-eligibility-criteria.

## ARBOVIRUSES AND TRANSFUSION IN NEW ZEALAND

In December 2014 NZBS introduced a range of measures to reduce the risk of transmission of arboviruses by transfusion.

Arboviruses are viruses that are transmitted by insects (arthropods) and infection normally occurs in the context of mosquito and tick bites taking place during overseas travel. There is good evidence that many of the viruses can be transmitted by transfusion and a number of countries, now including New Zealand, have introduced measures to reduce the likelihood of this occurring.

The three main viruses of current concern are West Nile virus, dengue and chikungunya.

Interest in West Nile virus was first raised during an epidemic in the United States and Canada that began in 1999. The epidemic progressively moved across the US from east to west over a period of 4-5 years. Evidence of transfusion transmission was identified early in the epidemic and measures quickly taken to introduce nucleic acid testing for the virus. Blood Services in North America routinely test all donations for evidence of the infection. The incubation period for the infection is typically up to 14 days following exposure. Blood Services outside of North America reduce the likelihood of transfusion transmission by deferring healthy donors for a period of 4 weeks following departure from the risk area. In recent years there have been an increasing number of cases of West Nile virus infection reported in Europe that have been acquired locally as opposed to occurring following travel to a risk area. This includes parts of Greece, Italy, Hungary and countries of former Yugoslavia. NZBS has now extended its donor deferral countries to include travel to these countries during the European mosquito season. No cases of West Nile virus have been reported in New Zealand.

Dengue infection occurs widely in tropical areas with regular outbreaks occurring in many Latin American, Asian and African countries. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash that is similar to measles. In a small proportion of cases the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs. The incubation period of dengue is similar to that of West Nile virus. A number of cases of transfusion associated dengue have been reported and there is good laboratory evidence of the virus being present in the blood of healthy donors in endemic areas. The number of reported cases of dengue infection in New Zealand has increased significantly in recent years. Cases are all linked to travel to endemic areas predominantly the Pacific Islands and South East Asia. Donors who have travelled to endemic countries are now deferred for a period of 4 weeks following departure from the risk area.

Chikungunya infection causes an illness with symptoms similar to dengue fever. The infection presents with an acute febrile phase of the illness lasting only two to five days, followed by a prolonged arthralgic disease that affects the joints of the extremities. The pain associated with chikungunya infection of the joints persists for weeks or months, or in some cases years. The infection is endemic in parts of Africa, India, South East Asia and the Philippines. Interest in the virus has increased following large scale outbreaks in the islands in the Indian Ocean, Singapore, Thailand and Malaysia during the last few years. A significant outbreak occurred in the Caribbean in 2014. There is also evidence of on-going transmission in the Pacific Islands with imported cases diagnosed in New Zealand during the last two years. There are no reports of cases of transfusion associated infection but it seems likely that this might occur. Donors who have travelled to risk countries are questioned for the presence of symptoms suggestive of the infection and deferred if these are reported.

A survey of donor travel was undertaken by NZBS during 2012/13. The primary aim of the survey was to assess the feasibility of introducing a standard deferral following overseas travel. This approach has been used successfully by the Netherlands and greatly simplifies the management of imported infections related to transfusion. The survey identified that 7.3% of donors had travelled outside of New Zealand in the period immediately before donation. This reduces to 3.2% if travel to Australia is excluded. The loss of donors associated with a standard deferral for any overseas travel was considered excessive given the known risk and a more targeted approach was then developed as discussed above. NZBS estimates that approximately 1% of donors will be deferred by these measures. A donor travel tool has been developed to enable donors to assess their eligibility to donate. This is available on the NZBS website (www.nzblood.co.nz). Initial results indicate that this has been effective with no increase in overall deferral rates seen since the implementation of the new measures and only small numbers of deferrals specifically linked to these viruses.