BLOOD ISSUES

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INTRODUCTION OF EXTENDED LIFE PLASMA (FFP-EL) INTO NEW ZEALAND

In December 2017, NZBS will be introducing Extended Life Plasma. This will provide an opportunity to improve the timeliness of delivery of thawed plasma in trauma and massive haemorrhage settings and will help larger hospitals to reduce discard rates of the thawed component.

Clinical Fresh Frozen Plasma (FFP) in New Zealand is currently produced from apheresis plasma given by male donors. Once thawed the component has a shelf life of 24-hours. There is increasing evidence to support the proactive early use of FFP in massive haemorrhage and trauma situations. Thawed FFP is provided as part of the Massive Transfusion Protocol (MTP) with the goal of achieving a 1:1 ratio of red cells to plasma during the immediate management of these clinical scenarios.

Two problems emerge in doing this. Firstly, the time taken to thaw FFP can delay the early availability of plasma and secondly, changing clinical circumstances can result in the thawed plasma not being transfused, resulting in expiry of the component.

NZBS has now received approval from Medsafe to extend the shelf life of thawed frozen plasma from 24-hours to 5 days (120hrs). The longer storage period for the thawed component is associated with a gradual reduction in non-labile coagulation factors, but this is considered unlikely to impact on the clinical effectiveness of the component.

However, extended life plasma (FFP-EL) will not be useful as a source of Factor VIII or Factor V since the level of these factors fall more rapidly. Clinical FFP is however, rarely, if ever, used for these indications in New Zealand.

Two approaches for the introduction of ELP exist. The first is that this replaces the current standard FFP component. This is the approach used in most large hospitals in Australia. In England, the use of ELP is restricted to patients with major haemorrhage or trauma with standard FFP being supplied for all other indications. In both countries, the use of ELP is not recommended for hospitals with limited trauma work.

New Zealand will follow the approach in place in Australia. Individual hospitals will supply thawed plasma either with a 24-hour shelf life (thawed FFP) or with a 5-day (120hrs) shelf life (FFP-EL) but not both. NZBS is currently working with individual hospital Blood Banks to determine which approach will be most appropriate. We anticipate that most major DHBs will elect to use FFP-EL. Smaller hospitals with low usage of thawed plasma may however decide to stay with the current 24-hour shelf life.

There are two potential risks associated with the extension of the shelf life of thawed plasma.

The first is that it might increase the risk of bacterial contamination. This is reduced by keeping the stored plasma at between 2 and 6 degrees Celsius in a dedicated blood refrigerator. There is however, no evidence from Australia or the UK that this is a major concern.

The second potential risk relates to leakage of plasticisers such as DEHP (Di (2-ethylhexyl) phthalate) into the plasma. This is a particular concern when plasma is transfused to neonates. Neonatal FFP is not normally used in massive transfusion settings and so no clinical benefit will arise from extending the shelf life. For this reason, NZBS will be maintaining a 24-hour shelf life for neonatal thawed plasma at all sites.

What about Cryoprecipitate?

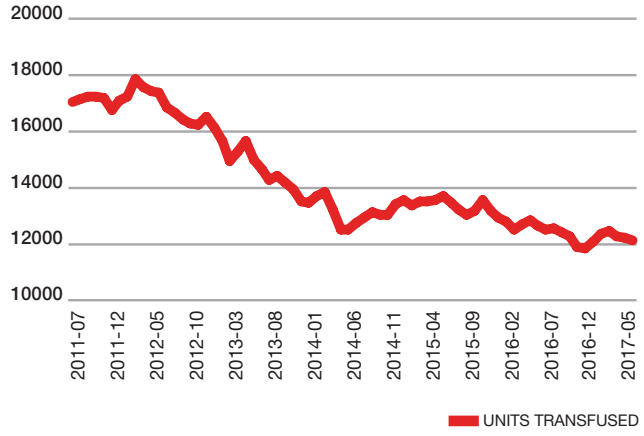
The shelf life of thawed cryoprecipitate is currently 4-hours with no plans to change this. There are two reasons for this. The component specification for Cryoprecipitate requires FVIII levels to be maintained at a specified level. This relates to its historic use in haemophilia treatment. Factor VIII is a labile coagulation factor and levels fall quickly once the component is thawed. Secondly, thawed Cryoprecipitate is stored at room temperature since refrigeration leads to protein precipitation. Storage at room temperature also increases the risk of bacterial contamination.

How much FFP is used in New Zealand?

The chart overleaf shows the amount of FFP transfused to patients over the 6-year period to the end of June 2017. The number of units transfused has fallen by 30% between April 2012 and April 2017. The reduction seen in the initial part of the period reflects a move to the use of Prothrombinex-VF in the management of warfarin reversal.

Currently 12% of thawed FFP is discarded. This can occur for a number of reasons, but most frequently occurs because the clinical status of the patient changes and FFP is no longer required. The introduction of FFP-EL should reduce the likelihood of this wastage occurring.

FIGURE 1 FFP UNITS TRANSFUSED JULY 2011 – JUNE 2017



The TRANSFUSE Study

Storage of red cells in liquid anti-coagulant results in predictable biochemical and morphological changes to the red cells over time. This 'red cell storage lesion' reduces the ability of the cell to transfer oxygen to the tissues and membrane changes that reduce deformability of the red cell with consequent reduction in the ability to traverse the microcirculation. Many, but not all, of these changes are reversible following transfusion. The clinical impact of the changes is controversial.

A number of studies have identified that transfusion of older red cells in various clinical settings are associated with adverse clinical outcomes. These studies were generally retrospective in nature and methodological questions were raised suggesting that the conclusions might not be appropriate. This is an important issue for those involved in transfusion medicine since, if the association between age of red cells at transfusion and clinical outcomes were to be confirmed, this would likely have significant impact on blood service activities. A series of randomised controlled trials, including the TRANSFUSE study, were developed to address the question 'is fresh best?'

The TRANSFUSE study investigated the use of 'standard issue' red cells compared with the freshest available red cells in almost 5000 critically ill patients receiving treatment in the Intensive Care Unit. The study was co-ordinated by the Australian & New Zealand Intensive Care Society (ANZICS). The results of the study published in the New England Journal of Medicine dated September 2017.

Reference:
http://www.nejm.org/doi/full/10.1056/NEJMoa1707572#t=article

Eight New Zealand hospitals participated in the study, which was supported by the Health Research Council of New Zealand. The study showed that the age of transfused red cells did not affect 90-day mortality among critically ill adults. These results mirror those of a number of other studies that focussed on other patient groups. The RECESS study that was published in 2015, focussed on patients undergoing complex cardiac surgery who were likely to receive transfusion of red cells. RECESS also found no difference in patient outcome.

Reference:
http://www.nejm.org/doi/full/10.1056/NEJMoa1414219

In 2007 the NZBS Fresh Blood Policy was developed. The aim was to standardise the approach used by hospital Blood Banks to the provision of fresher red cell components. The policy is accessible on the NZBS website:

Reference:
https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/NZBS-Policy-on-Use-of-Fresh-Blood-111P074.pdf

The policy will be reviewed early in 2018 to take into account the results of TRANSFUSE and RECESS. The review will include a sector consultation process utilising the Hospital Transfusion Committee network.

Annual Haemovigilance report

The 2016 Annual Haemovigilance Report is now available on the NZBS website. This can be accessed at:

Reference:
https://www.nzblood.co.nz/clinical-information/haemovigilance-programme/haemovigilance-annual-report-2012/

The report provides a summary of adverse events reported to NZBS during 2016 and information on trends in component use. A hard copy can be obtained by emailing Karen Martin, (karen.martin@nzblood.co.nz).

Residual risk of transmission of major blood borne viruses

The 2016 Haemovigilance Report includes a reassessment of the risk that blood components that have been properly tested, might transmit major blood borne viruses such as HIV and hepatitis B and C. This is calculated based on data on the frequency of infections seen in both first time and returning donors. This data, combined with information on the performance of the screening tests used to accredit the donations, enables us to assess the risk that a donation is in the window period and hence potentially able to transmit the infection to the recipient. Detailed information on the model used is provided in the report.

The estimated risk of 'window period' transmissions are shown in the table below along with 95% confidence intervals. The risks are very low and consistent with the observation that transmission of neither HIV nor HCV has been documented in New Zealand since testing began, for HIV (1985) and for HCV (1992).

TABLE 1 RESIDUAL RISK ESTIMATES FOR HUMAN IMMUNO-DEFICIENCY VIRUS, HEPATITIS B AND HEPATITIS C TRANSFUSION-TRANSMITTED INFECTION IN NEW ZEALAND

Infection	Mean Risk	95% Prediction Interval
HIV	1 in 9.55 million	1 in 3.09 to 26.24 million
Hepatitis C	1 in 7.82 million	1 in 4.06 to 14.04 million
Hepatitis B	1 in 0.85 million	1 in 0.47 to 1.57 million

Assessing the risk of transmission of hepatitis B is more complex than for the other two viruses. This is because the model used to assess the risk, does not take into account the risk of occult hepatitis B. This is a state where the liver is infected by hepatitis B but the virus is only multiplying intermittently and at low levels. As a result, the screening tests for hepatitis B are negative, but very low levels of viral DNA, enough to cause infection, may still be present. The introduction of testing for the virus (HBV DNA) has greatly reduced, though not eliminated, the risk of transmission of hepatitis B by this mechanism. NZBS currently estimates that the risk of transmission of HBV is in the order of 1 in 300,000 transfusions or once every 2-3 years.

The overall risks of transmission of these viruses compares well with that published by blood services in other similar countries including the United Kingdom and Australia. Comparative data is provided in the Haemovigilance Report.

Warfarin Reversal app

NZBS supported the development of an app to guide management of people on warfarin who require reversal of the anticoagulant effect. Dr Paul Harper of HealthObs developed the app, which is available for both Apple and Android systems. The original version of the app was developed in 2013. It will not work on iOS 11.0.3. A new version is now available and can be accessed from the Apple store or via this link:

Reference:
https://itunes.apple.com/nz/app/reversing-warfarin/id641461083?mt=8

UK Proposals to reduce deferral period for MSM – Implications for NZBS

During July 2017, the UK Advisory Committee on the Safety of Blood, Tissue and Organs (SaBTO) issued a report outlining proposals for changes to the UK donor deferral criteria for 'high risk' behaviours including the deferral for male-to-male sex (MSM). The report is accessible at:

Reference:
https://www.gov.uk/government/publications/blood-tissue-and-cell-donor-selection-criteria-report-2017

These deferrals are highly sensitive and NZBS monitors international developments closely. The UK plan to reduce their current 12-month deferral to 3 months in early 2018.

NZBS implemented a 12-month deferral for MSM in December 2015 in line with recommendations developed by an independent expert group chaired by Emeritus Professor Charlotte Paul, accessible at:

Reference:
https://www.nzblood.co.nz/assets/News/Final-report-to-NZBS-behavioural-donor-deferral-criteria-review.pdf

The period of deferral is similar to that in place in many other countries including the USA, Canada, Australia, Ireland and the Netherlands.

NZBS is aware of a number of reviews being undertaken by blood services across the globe. There is an increasing recognition that reducing the length of the deferral will not significantly increase the opportunity for MSM to donate and an acknowledgement that an individual risk based approach is likely preferable to the current time based deferral. The challenge for blood services will be to define individual risk based assessment processes that are at least as effective as the current approach. We are monitoring the situation closely and will reconvene an independent expert panel to reassess the current deferrals when appropriate.

National Tissue Typing Laboratory introduces Next Generating Sequencing

The National Tissue Typing Laboratory based in the Auckland Blood Centre is responsible for the tissue typing of all patients and potential donors, prior to kidney, pancreas, heart, and lung or haematopoietic cell transplantation in New Zealand. Tissue typing is an essential component of donor compatibility assessment and selection prior to transplantation, and involves the characterisation of the human leucocyte antigen (HLA) genes and proteins. The HLA proteins are expressed on nearly all cells in the body and are part of the human immune system. Differences in HLA proteins between transplant patients and donors can lead to either rejection of the transplanted organ or graft versus host disease after haematopoietic cell transplantation.

In addition to the transplant related work, the Tissue Typing Laboratory types patients suspected of having an illness associated with a particular HLA type, patients who need medications where there may be a hypersensitive drug reaction if the patient has a particular HLA type and patients who are refractory to platelet transfusions. The laboratory also supports testing for donors joining the New Zealand Bone Marrow Donor Registry (NZBMDR), NZBS apheresis donors and the investigation of suspected cases of transfusion related acute lung injury (TRALI).

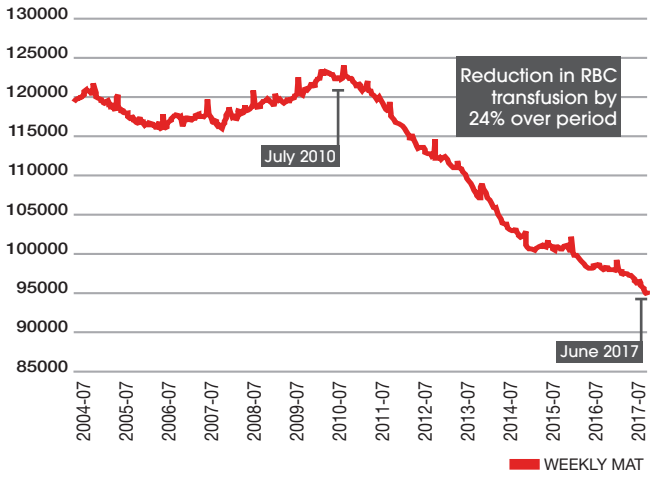
On 1 July 2017, the Tissue Typing Laboratory introduced a major change in technology, moving to next generation sequencing (NGS) as the main HLA typing method for transplant patients and donors. Prior to 1 July, a combination of different methods was used, requiring multiple assays for each sample, to type five HLA genes at a medium to high-resolution level. NGS technology enables the typing of eleven HLA genes at a high-resolution level in one assay. This is much more efficient and meets the clinical needs for transplantation.

Since the introduction of NGS testing, the laboratory has identified 19 potentially new HLA variants, having not been previously reported and would not have been detected with the previous typing methods used. The introduction of NGS has also improved the efficiency of the laboratory with a significant reduction in the number of samples requiring repeat testing, and improved turnaround times for provision of reports. Most importantly, the introduction of NGS is increasingly recognised as the international standard for tissue typing and ensures that the systems used for testing in New Zealand are of an appropriate standard.

Changing Pattern of Red Cell Utilisation

Clinical use of red cell components has also reduced significantly over the last 10 years with a 24% fall in the number of red cells transfused annually in New Zealand from July 2010 to July 2017.

FIGURE 2 RED CELL COMPONENTS TRANSFUSED OVER TIME



The reduction in red cell transfusion rate reflects a move to a more restrictive haemoglobin trigger for red cell transfusion. A number of randomised controlled studies have shown that the use of a restrictive trigger results in clinical outcomes that are at least as good as when a more conservative (i.e. higher) transfusion trigger is used. The use of a restrictive threshold for transfusion has been widely promoted at a number of DHBs using the 'Why use two when one will do' campaigns in recent years.

The decision to transfuse a patient should not be determined solely on a patient's haemoglobin level or trigger, but should be based on assessment of the patient's clinical status. In most post-operative patients, transfusion should be considered when the haemoglobin level falls to 70g/L. A higher figure might be appropriate in patients with acute coronary syndrome or cerebrovascular disease. Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level. More information on restrictive transfusion strategies can be obtained from the Australian National Blood Authority website

Reference:
https://www.blood.gov.au/system/files/documents/companion-24-pbm-guidelines.pdf

The implementation of Patient Blood Management (PBM) approaches has also contributed to the reduction in use of red cell components. In particular, the use of intravenous iron infusions in patients with iron deficiency prior to elective surgery has been shown to be highly effective in reducing the likelihood of subsequent transfusion.

Similar falls in red cell transfusion rates have been reported in most other developed countries. The challenge for Blood Services, including NZBS, is to try to predict how low the rate might go.