Blood and transfusion medicine update

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National Massive Haemorrhage Pathway (MHP) Redesign

A group of blood and transfusion representatives from regional and tertiary hospitals throughout New Zealand have created a new national MHP. The aim of the project is to simplify and standardise all three MHP's for all healthcare workers no matter where in New Zealand they work. The aim is to also improve communication between blood bank and the location of the transfusion and reduce wastage of blood products.

The MHP incorporates all three types of massive transfusions that can be activated:

a) Standard MHP
b) Code crimson / Trauma MHP
c) Obstetric MHP

The major changes within this project include:

1. **The introduction of a "Stat Pack" for all three pathways**. This gives clinicians immediate access to blood products with the opportunity to transfuse, then stop and reassess the patient. If there is ongoing bleeding and signs of shock, there can then be formal activation of the MHP. However, if the patient has stabilised or bleeding has ceased, there has been no further thawing of blood products and therefore no wastage.

   From international statistics we know that 65% of major trauma does not require more than one unit of RBC's (Holcomb 2015). These statistics are similar amongst other New Zealand hospitals, and that is why we have instituted these changes. However, if the treating clinician believes this is a major haemorrhage that requires immediate activation of the MHP, this can be done, the stat pack will be issued and thawing of box one will be immediate.

2. **The introduction of a MHP/Transfusion Co-ordinator**. This is a separate role to the team leader, this person is the liaison between the point of the resuscitation and blood bank. Their list of tasks are on the back page of the MHP pathway. Most importantly they are there to improve communication with blood bank and update them when formal activation of the pathway is required, location change of the patient, ceasing the MHP and moving to targeted transfusion.

3. **Simplification of packs 1/2/3**, where packs 2/3 become the alternating products until the MHP is stopped and commencement of targeted transfusion.

4. **Stat dose of 2g tranexamic acid** in code crimson/trauma.

Successful trauma management is not just about the detail of blood product ratios of a MTP but is rather a co-ordinated approach to rapid assessment and definitive damage control surgery. While this is occurring there should be resuscitation with blood products that represents the reconstitution of whole blood with minimal crystalloid administration.

Adult Massive Haemorrhage Pathway

Massive Bleeding PLUS
Shock Signs or **HR > 120** or **SBP < 90**

Code Crimson	Standard MHP	Obstetric MHP
Trauma + ABC Score ≥ 2 + senior clinician approval	Medical or Surgical Bleeding	
2g Tranexamic Acid	**1g Tranexamic Acid**	**1g Tranexamic Acid**

Send Group + Screen
Initiate: Call Blood Bank, Provide Patient Details + Request

Crimson Stat Pack	Stat Pack	Obstetric Stat Pack
2 RBC, 2 FFP	2 RBC	2 RBC

Reassess: Ongoing Massive Bleeding + Shock: Call Blood Bank
Activate MHP + Identify MHP Coordinator

Code Crimson	Standard Pack 1	Obstetric Pack 1
Straight to Pack 2	2 RBC, 2 FFP	2 RBC, 3 Cryo

Pack 2
4 RBC, 4 FFP
3 Cryo

1g Calcium with every pack

Pack 3
4 RBC, 4 FFP
1 Platelet*

Alternating packs 2 & 3 until bleeding slowed

Then stop MHP, and start targeted transfusion

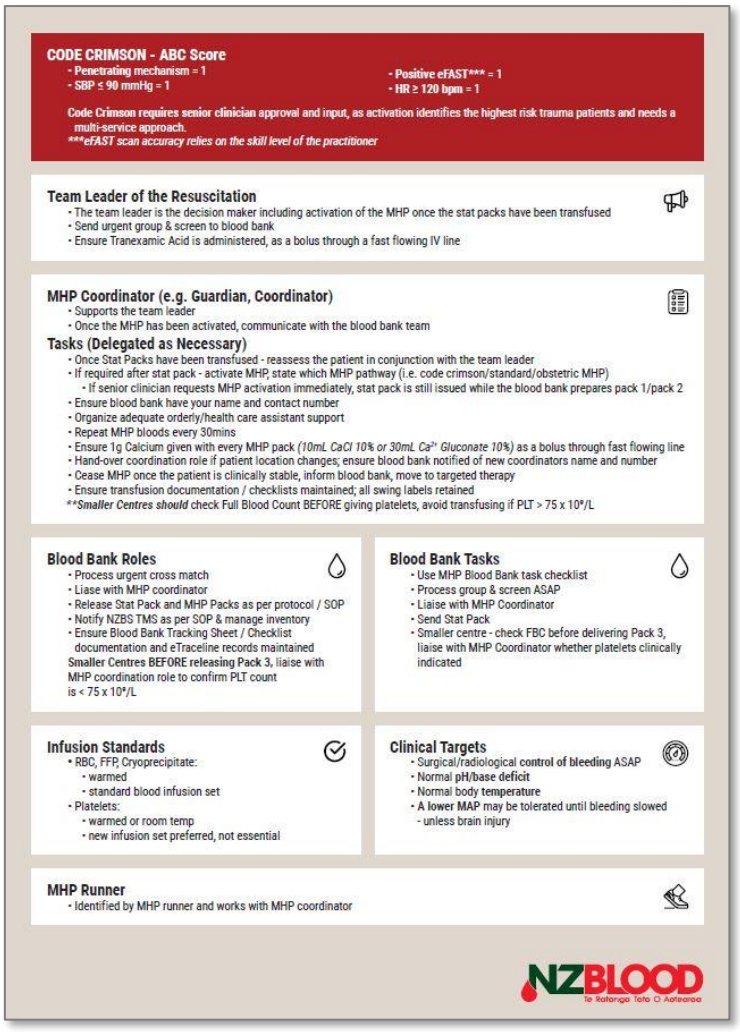
Bloods:
- **repeat every 30min**
- Blood gas
- iCa^{2+}
- FBC
- Coags
- Fibrinogen
- Viscoelastic if available e.g. TEG®

Coagulation Targets	If Not, Give
PR < 1.5 | APTT < 40	4 U FFP
Fibrinogen > 2g/L	3 U Cryoprecipitate
Platelets > 75 x 10^9/L	1 U Platelets**
Ionised Ca^{2+} > 1.1 mmol/L	1g Calcium

Obstetric Haemorrhage
- Manage Tone, Trauma, Tissue, Thrombin causes of haemorrhage
- Repeat TXA 1g 30 min after initial dose if significant ongoing bleeding

*See notes on page 2

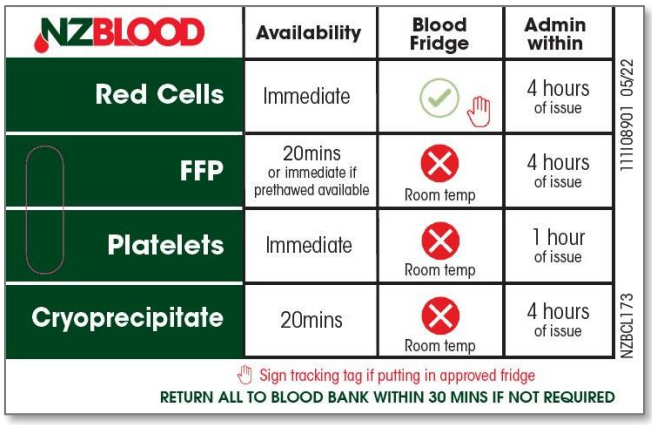
NZBLOOD
Te Ratonga Toto O Aotearoa



Blood Handling Rules Lanyard

It is impossible to remember all the rules around the safe handling of blood products, when you must return them by in order to be reissued and not wasted. Therefore, we have designed a simple lanyard as a reference tool for all healthcare workers nationwide. These are based on New Zealand Blood Service (NZBS) rules, (which most non-NZBS blood banks also follow).

We hope to one day have a solution to the manual swing tag sign in/out on the unit of RBC's when they enter/exit a blood fridge, but at this stage, it's still a manual task. Without evidence of the cold chain on the swing tag, the RBC will be discarded.



NZBLOOD	Availability	Blood Fridge	Admin within
Red Cells	Immediate	✓	4 hours of issue
FFP	20mins or immediate if prethawed available	✗ Room temp	4 hours of issue
Platelets	Immediate	✗ Room temp	1 hour of issue
Cryoprecipitate	20mins	✗ Room temp	4 hours of issue

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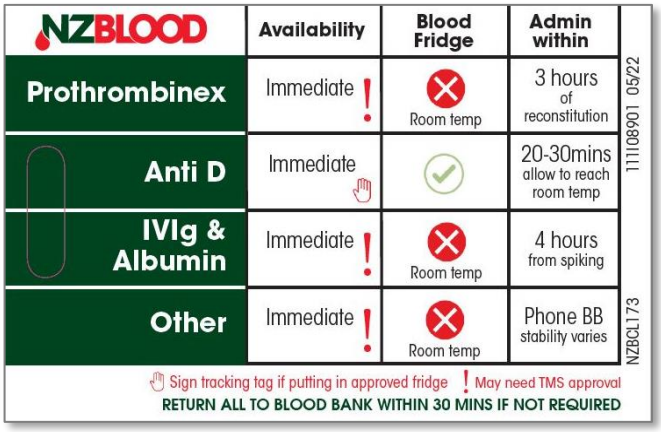
Sign tracking tag if putting in approved fridge
RETURN ALL TO BLOOD BANK WITHIN 30 MINS IF NOT REQUIRED



NZBLOOD	Availability	Blood Fridge	Admin within
Prothrombinex	Immediate !	✗ Room temp	3 hours of reconstitution
Anti D	Immediate	✓	20-30mins allow to reach room temp
IVIg & Albumin	Immediate !	✗ Room temp	4 hours from spiking
Other	Immediate !	✗ Room temp	Phone BB stability varies

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Sign tracking tag if putting in approved fridge ! May need TMS approval
RETURN ALL TO BLOOD BANK WITHIN 30 MINS IF NOT REQUIRED

Top tips for saving blood products:

- **RBC's** – Ensure the "swing tag" is signed in/out of the blood fridge when storing them in your operating room environment.
- **RBC's** – Ensure they are never out of the fridge for more than 30 minutes.
- **FFP** – You can "thaw and hold" FFP in your blood bank in situations where you can't predict if FFP will be required, and if you do need it, it is time critical. This is especially helpful in cardiac surgery, liver surgery and trauma when moving on to targeted transfusions. If FFP is not needed, then it can stay in blood bank and be moved to "extended life plasma" (ELP), where it has a five day fridge life and can be reissued to another patient.
- **Cryoprecipitate** - Only thaw cryoprecipitate if it's going to be needed. If you thaw it and then don't need it, it only has four hours to be reissued to another patient. The cryoprecipitate would most likely be wasted since reissuing is unlikely.

Prices 2022

Below are the costs of each unit of blood product supplied from NZBS to our hospitals. This does not include consumables, nursing or administration time.

Red cells	$337.10
FFP	$247.28
Prothrombinex (500IU)	$346.39
Cryoprecipitate	$464.28
Platelets	$948.48
Riastap (fibrinogen concentrate)	$852.49

Future Blood Product Changes

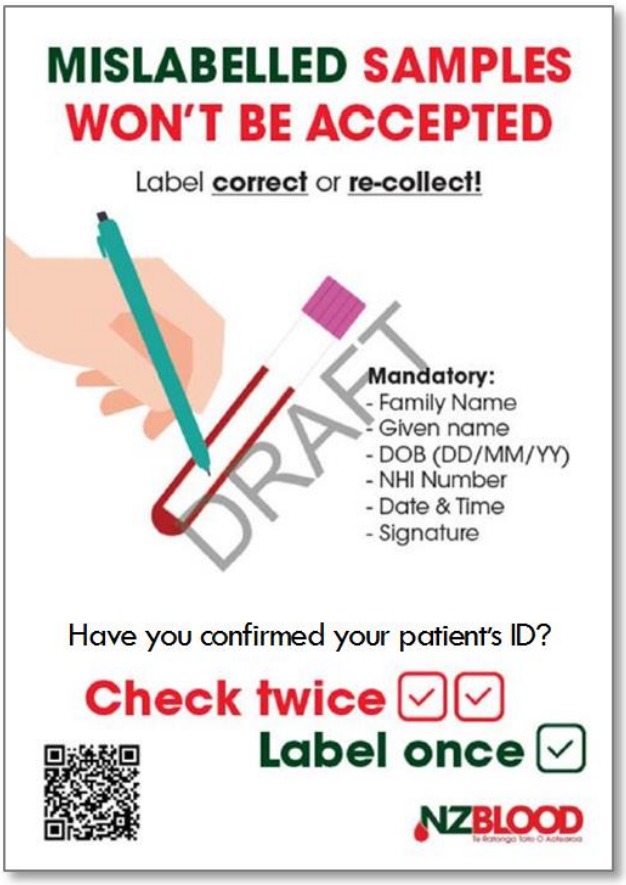
Prothrombin complex concentrates (PCC's) e.g. Prothrombinex.

With the upgrade of CSL Behring plant in Melbourne, we will have Beriplex NZ, a four factor PCC containing factors II, VII, IX, X and the important balanced anticoagulants protein S and C. This will bring us into alignment with the rest of the world with four factor PCC. This will enable us to apply international data and research on PCC use in areas such as cardiac surgery, liver transplant and massive bleeding. We expect Beriplex NZ to arrive end of 2024.

Albumin

Albumin will be changing from Albumex 4% to Alburex NZ 5%, with Albumex 20% staying at the current concentration but with a name change to Alburex NZ 20%.

Group and Screen Labelling Errors



As anaesthetists, occasionally we have to do a group and screen on our patient. We fill out the request form, awkwardly handwrite on the tube, send the sample off in the Lamson tube, then await the phone call from blood bank saying you've done it wrong, the sample is rejected and you have to do it all over again.

Unfortunately things are about to get harder. From September 2022 blood banks around New Zealand will no longer accept minor and moderate errors. Yes, most of us have been getting away with minor and moderate errors up until now. The **mandatory** information that must be on the pink group and screen tube is:

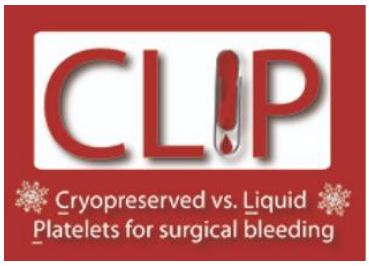
- Family name
- First name
- DOB (DD/MM/YY)
- NHI number
- Date and time
- Initial

This requirement is to reduce the frequency of wrong blood in tube events (WBIT) and ensure the patient and their blood group has been correctly identified. A WBIT event can lead to the wrong blood group being transfused to the patient and death; we have had one of these in a large city in last few years.

A working group is looking for a better solution to the arduous and awkward process of handwriting group and screens tubes and forms, with the introduction of electronic bedside labelling, much like when you have a blood test done at Labtests. This will require money and IT support, hopefully something that will be supported with Health NZ.

<u>Cryopreserved platelets (CPS)</u>

Platelet transfusion is a life-saving component in the treatment of major bleeding in such scenarios as trauma, major surgery, obstetric emergencies and acute medical conditions. The main issue with our current platelets formulation is their short shelf-life of only seven days. This limits the ability to keep an adequate supply at medium and small hospitals. In addition, almost 30% of platelets are wasted each year because they expire before administration. This not only results in significant financial loss, in excess of $5million per year (each bag costs $948), but it's also a discourtesy to those who donate platelets.



Unlike red blood cells, platelets cannot be refrigerated as this significantly impairs their function, and room temperature storage (RTS) for > 7 days is limited by the risk of infection.

Unlike refrigeration, and somewhat surprisingly, cryopreservation of platelets at -80°C increases the shelf life to two years. If cryopreserved platelets are as safe and effective as liquid-stored platelets it would allow smaller hospitals to easily provide platelet transfusions, and would reduce platelet wastage, and possibly produce better patient outcomes through more effective haemostasis.

There are two clinical trials which are relevant obligatory steps which need to be completed before cryopreserved platelets will be ready for use in New Zealand.

CLIP-I (NZ) was a pilot study conducted by Auckland City Hospital, Cardiovascular ICU Research and the NZBS. This pilot assessed production and distribution logistics, feasibility and safety aspects of CPS. In addition, the results of the trial were used by NZBS to support the successful product registration

of CPS with MEDSAFE. Over 12 months, 91 patients were enrolled and 23 of these received platelets (25% of enrolled patients) and were randomised to either RTS platelets or CPS. There were no differences in outcomes between the groups. CLIP-1 NZ also demonstrated that NZBS was able to manufacture and distribute CPS and that these platelets were safe for patients. CLIP-I (NZ) has now been published.

CLIP-II (NZ) is now running in all five cardiac surgery centres in New Zealand. It is multicentre, blinded, randomised controlled, non-inferiority trial of CPS vs. conventional RTS platelets for the management of post-operative bleeding in patients undergoing cardiac surgery. We will need to recruit 800-900 patients in order to enroll 230 patients (recruitment rate around 25%) in this study.

If this research demonstrates that CPS are not inferior to traditional platelets for the control of major bleeding occurring during cardiac surgery, then their use will be extended to other situations where urgent platelet transfusion is indicated, and they will be made available in hospitals that do not currently keep them on site.

The research impact includes:

1. Reduction in inequity. Patients presenting to smaller hospitals will have access to platelets in a timely manner so that the latest MTP's can be followed which have been shown to improve outcomes in diverse clinical scenarios including trauma, major surgery and obstetric emergencies.
2. Significant cost savings.
3. Less wastage of donated platelets.

Four Factor PCC's for New Zealand and Australia AND the use of PCC's in non-warfarin contexts

Australia and New Zealand are the only countries to exclusively have the three factor prothrombin complex concentrate (PCC) Prothrombinex. Prothrombinex contains factors II, IX, X with variable smaller amounts of VII, and heparin 192 iu/vial. Four factor PCC's contains factors II, VII, IX, X and protein S and C. This product will be introduced into New Zealand towards the end of 2024, replacing our current Prothrombinex.

As we all know PCC's are routinely used for reversal of warfarin, however now there is growing evidence for PCC use in trauma and cardiac surgery.

A recent systematic review of the use of PCC's for the treatment of bleeding in trauma patients, showed that PCC's could be a beneficial adjunct during an MTP in addition to FFP. In trauma, PCC's combined with FFP showed reduced mortality when compared to FFP alone. The dose range for this was between 10-50 iu/kg, and there was no difference in mortality based on PCC dose. PCC's also showed a reduction in RBC transfusions when compared to transfusions with no PCC's. There was no difference in thromboembolic events between the two groups (van den Brink 2020;18). A standard 20 iu/kg dose in a 70kg patient costs about $1000.

A Cochrane review will be published this year on PCC use in cardiac surgery. Again, this shows a reduction in units of RBC transfusion, reduction in the incidence of RBC transfusion with no increased incidence of thrombotic events. We now routinely use PCC's in high-risk cardiac surgery who cannot tolerate the volume associated with FFP in cardiac surgery at Auckland City Hospital (Hayes 2020).

Cytosorb – For the emergency removal of Ticagrelor and Rivaroxiban

With no reversal available for ticagrelor and rivaroxaban, this poses a challenge for clinicians treating a patient who is taking one of these drugs who also has life-threatening bleeding such as upper GI bleeding, intracranial bleeding, ruptured abdominal aneurysm or is requiring emergency cardiac surgery.

Rivaroxaban is not dialysable as it is highly protein bound (95%), and can be expected to have decreased by more than 90% but only after four half-lives, i.e. approximately 28 hours (range 20 - 36 hours) in a patient with normal renal function. This is too long to wait in a life threatening bleeding context. Andexanet Alpha (in the USA) is a specific reversal agent for this drug but is not available in Australasia, costs over $60,000 for a bolus and small infusion dose, and there are safety concerns regarding its prothrombotic effect. Prothrombinex will only partially reverse the effects of rivaroxaban.

Ticagrelor is a reversible inhibitor of ADP on platelets, has no reversal agent available, and if any platelets are transfused to a patient on this drug in a bleeding context these platelets will in turn become inhibited.

A novel way of removing these drugs is using Cytosorb. This 300 ml cartridge is filled with porous polymer beads which adsorbs drugs with a size less than 55 kD. This requires a vascath, a dialysing circuit allowing a blood flow of around 150-250 ml/min and a pump to circulate the blood. The approximate cost is $800-$1000, which is similar to a bag of platelets.

So far this has successfully been used in cardiac surgery (where it is used while on cardiopulmonary bypass) both in Auckland and Wellington with approximately 20 patients at each site. This provides an option for those extreme cases of life-threatening bleeding caused by these two drugs and which is not controlled by other drug, blood, interventional or surgical means.

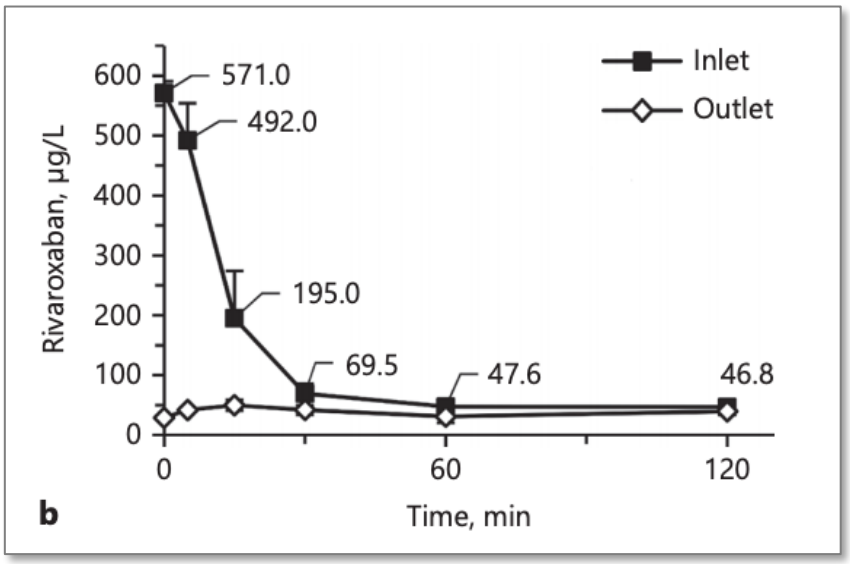


Figure 1 Invitro recirculation model showing inlet/outlet rivaroxaban plasma concentrations

References

1. John B. Holcomb, MD1, PhD2 Barbara C. Tilley, PhD2 Sarah Baraniuk, and et al. 2015. "Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma The PROPPR Randomized Clinical Trial." *JAMA* 313(5):471-482.

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3. van den Brink, D. Wirtz, M. Neto, A. Schochl, H. Viersen, V. Binnekade, J. Juffermans, N. 2020;18. "Effectiveness of prothrombin complex concentrate for the treatment of bleeding: A systematic review and meta-analysis." *Journal Thrombosis and Haemostasis* 2457-2467.