Guideline

Blood Product Transfusion in the Newborn

Document No: RPAH_GL (year number) _ Number (sequential akin to DOH)

Functional Sub-Group: Clinical Governance
Corporate Governance

Summary: Describes the indications for and management of transfusion of blood products in the newborn.

National Standard: Standard 1: Governance for Safety and Quality in Health Service Organisations

Policy Author: Nick Evans. Senior Staff Specialist in Newborn Care

Approved by: RPA Newborn Care Guideline Development Committee

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Previous Review Dates: June 2000

Note: Sydney Local Health District (LHD) and South Western Sydney LHD were established on 1 July 2011, with the dissolution of the former Sydney South West Area Health Service (SSWAHS) in January 2011. The former SSWAHS was established on 1 January 2005 with the amalgamation of the former Central Sydney Area Health Service (CSAHS) and the former South Western Sydney Area Health Service (SWSAHS).

In the interim period between 1 January 2011 and the release of specific LHN policies (dated after 1 January 2011) and SLHD (dated after July 2011), the former SSWAHS, CSAHS and SWSAHS policies are applicable to the LHDs as follows:

Where there is a relevant SSWAHS policy, that policy will apply

Where there is no relevant SSWAHS policy, relevant CSAHS policies will apply to Sydney LHD; and relevant SWSAHS policies will apply to South Western Sydney LHD.
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1: Transfusion of blood products in the newborn.

Introduction:
The indications for the administration of blood products in newborns are:

1. Emergency blood transfusion for acute blood loss which, if severe enough, leads into the:
   - Massive Transfusion Protocol.
2. Top up transfusion for anaemia, usually in the very preterm baby.
3. Platelet transfusion for thrombocytopenia.
4. Plasma and clotting factors for coagulopathy.
5. Exchange transfusion for risk of severe jaundice (see separate guideline).

2. Emergency blood transfusion for acute blood loss:

2.1 Aetiology: Hypovolaemia from acute blood loss is uncommon in the newborn but early recognition and management can be life saving. Most of the causes, with the exception of subgaleal haemorrhage occur during the intrapartum period so will present at birth. Causes include:

   - **Vasa Praevia** with fetal vessel damage at rupture of membranes. Low and velamentous cord insertion may have been identified on ultrasound in these pregnancies but they present with brisk antepartum blood loss at rupture of membranes.
   - **Feto-placental haemorrhage** this is seen in babies born with a tight nuchal cord or, occasionally, after vaginal breech deliveries. In both situations, slow compression of the cord obstructs the umbilical vein before the arteries, so blood pools in the placenta. If the cord is then cut to facilitate delivery, this blood is trapped in the placenta and the baby is born hypovolaemic. This is a difficult diagnosis because the blood loss is occult.
   - **Acute feto-fetal haemorrhage** can occur in monochorionic twins during labour, usually characterised by sudden change in the fetal trace of one twin and one very pale twin and one very pink twin at delivery. Chronic twin anaemia polycythaemia sequence (TAPS) is more common than acute and also results in one pale and one pink twin.
   - **Acute feto-maternal haemorrhage** is more commonly chronic than acute but should be considered. There are often no clinical clues to this because the blood loss in occult across the placenta. Diagnosis is based on flow cytometry to identify fetal blood cells in the maternal circulation.
   - **Subgaleal Haemorrhage** can be significant enough to cause hypovolaemia shortly after birth but more usually evolves over the early postnatal hours (see guideline). Diagnosis is clinical with the characteristic fluid-filled leather bag swelling on the scalp which crosses suture lines.
   - **Placental Haemorrhage** can occur spontaneously but more commonly when a caesarean section incision has to go through the placenta.
   - **Postnatal Spontaneous Haemorrhage;** This is usually due to congenital or acquired coagulopathy such as from vitamin K deficient haemorrhagic disease of the newborn or de novo haemophilia. These can present as acute blood loss from the GI tract or intracranially.

2.2 Diagnosis: Pallor is the dominant clinical feature of the baby born after an acute fetal bleed but this is non-specific because anaemic babies and asphyxiated babies are also pale at
birth. It is important to differentiate normovolaemic chronic anaemia from hypovolaemic acute anaemia. Both result in a clinically pale baby and both will have a low haematocrit (PCV<40%). The following clinical features may be present after acute blood loss.

- A clinical history of an antenatal bleed, particularly at rupture of membranes or if caesarean delivery has to occur through the placenta.
- Clinical signs include tachycardia and faint heart sounds.
- The baby has a low haemoglobin or haematocrit. In an emergency, consider the haemoglobin result on the blood gas machine read out.
- Cardiac ultrasound, if available, provides the most accurate differentiation. The chronically anaemic baby will have a dilated heart while the hypovolaemic baby will have a small chambered under-filled heart.

Legend to pictures: The pictures shows the difference in ventricular volumes before and after 20mls/kg of volume expansion in a baby hypovolaemic from a perinatal bleed.

2.3 Management is focused on urgent volume replacement with saline and uncrossmatched O-negative blood. So if there is a high level of suspicion for acute perinatal blood loss:

- Call for senior neonatal medical assistance.
- Call blood bank on 57831 (Massive Transfusion Hotline) (number on resuscitaire) and place an urgent request for a unit of uncrossmatched, non-irradiated, O-negative blood.
- Send a runner to the blood bank window to collect it. (The location of the blood bank window is Level 5 of the main building in the corridor with the outpatient pharmacy. Go past the discharge lounge, past the outpatient pharmacy and past the medical centre pathology blood collection to the blood bank window. There are bright red signs in the corridor that say ‘blood bank reception’ with arrows indicating where to go).
- Establish intravenous access with an umbilical venous catheter.
- If there is time, take blood for full blood count, film, coagulation studies, group and cross match and put some blood on a newborn screening card.
- Give 20 mls/kg of N-saline over 5 to 10 minutes or more rapidly if the baby is in extremis.
- When available 20 mls/kg of O-negative blood over 5 to 30 minutes depending of estimated severity of the hypovolaemia.
- Transfer to the NICU and assess volume status with vital signs (heart rate and blood pressure) and filling status of ventricles on cardiac ultrasound.
- Check and correct any coagulopathy.
- Give further transfusion of cross matched blood as indicated.
- If this is a postnatal bleed, consider vitamin K deficient haemorrhagic disease of the newborn. Confirm prophylactic vitamin K was given and, if not, administer.
2.3.1 Massive Transfusion Protocol.

2.3.1.1 Background: In situations where there is ongoing severe blood loss with need for blood replacement, it is well recognised a coagulopathy can develop because haemostatic factors (clotting factors and platelets) in the blood are not being replaced. The causes of this coagulopathy are complex and poorly understood. See reference 1 for further reading. This transfusion related coagulopathy can lead to a vicious circle of blood loss. In specialties where such critical bleeding is common (trauma and surgery), a reactive approach to transfusion related coagulopathy has been superseded by pro-active massive transfusion protocols. In massive transfusion protocols, rather than wait for the coagulopathy to develop, clotting factors and platelets are replaced pro-actively according to a defined protocol. Most massive transfusion protocols have been developed for adults with a few for children that have been stretched down into the neonatal period on a transfusion volume per kg body weight basis. There is no literature on the use of massive transfusion protocols in the newborn but the principles make sense and probably still apply.

2.3.1.2 Definition: The following criteria have been proposed as situations that should trigger a massive transfusion protocol.\(^1\)

- Transfusion of more than 50% of total blood volume (40-45mls/kg) in less than 4 hours.
- Transfusion of more than 100% of total blood volume (85mls/kg) in 24 hours.
- Need to replace more than 10% of total blood volume per minute.

2.3.1.3 Aetiology: Ongoing critical bleeding is rare in non-surgical neonatology. Subgaleal haemorrhage would be the main critical bleeding pathology in the newborn. This is rare and routine scalp observations after instrumental delivery should further reduce this risk. However, when diagnosed late, transfusion associated coagulopathy and ongoing critical bleeding can occur.

2.3.1.4 Protocol: The flow chart below outlines a suggested guideline for managing critical bleeding and is adapted from the review of Diab et al\(^7\) on massive transfusion in children and neonates and the Australian Patient Blood Management Guidelines.\(^2\) The flow chart is based on two guiding principles:

- That if there has been a large bleed requiring transfusion up to 40mls/kg but there is no ongoing haemorrhage, then the baby should be investigated for transfusion associated coagulopathy and derangements can be treated reactively.
- That if there is an ongoing blood loss requiring blood transfusion of more than 40 mls/kg then coagulopathy should be measured but treatment should not be delayed by waiting for the results. Coagulopathy should be assumed and blood products given in cycles of Transfusion Package A (RBCs, platelets and FFP) alternating with Transfusion Package B (RBCs, platelets and cryoprecipitate) with volumes as detailed in the flow chart.

Two further interventions which are not detailed in the flow chart are:

2.3.1.5 Recombinant factor VII. The evidence of use of recombinant factor VII is mainly from adults and this is not recommended for routine treatment. The National Guidelines\(^2\) indicate that use can be considered when the following 4 criteria apply:

1. Uncontrolled bleeding in a salvageable patient and
2. Surgical and/or radiological measures to control bleeding have failed and
3. There has been adequate blood product replacement and
4. pH >7.2 and temperature > 34°C
2.3.1.6 **Tranexamic acid** is an antifibrinolytic. The evidence of effect in controlling bleeding is mainly based on surgical bleeding, particularly cardiac surgery where it has been shown to reduce bleeding and need for blood products. There is no evidence or even case reports on its use in non-surgical bleeding such as sub-galeal haemorrhage.

The suggested dosage is 15mg/kg loading dose over 10 minutes followed by infusion of 2mg/kg/hr until the bleeding stops.
Compliance with this Guideline is recommended
4. Top up blood transfusions for anaemia:

This is the commonest indication for blood transfusion in neonatology,

- Anaemia of Prematurity: This is common in the very preterm baby and is caused by delayed red cell production from an immature bone marrow and iatrogenic blood loss from repeated sampling.
- Fetal anaemia: less commonly in babies born after non-haemolytic fetal anaemia from causes such as feto-maternal haemorrhage and twin anaemia polycythaemia syndrome or red cell production problems such as Parvovirus infection or Diamond-Blackfan Syndrome (primary red cell aplasia).

4.1 Anaemia of Prematurity.

Anaemia of prematurity is caused by delayed red cell production from an immature bone marrow and iatrogenic blood loss from repeated sampling. The risk is dominated by lower birth weight (hence lower blood volume and illness severity hence need for sampling). Clearly both risk factors go together.

4.2 Red cell transfusions in preterm babies at RPAH 2011 to 2016.

The following graph is derived from RPAH data from July 2011 to June 2016 and shows, for each year, the total number of babies transfused red cells and the total number of red cell transfusions. Seventy five percent of all transfusions are given to babies born before 31 weeks. There is a trend to less transfusions over the last five years.

The major predictor for need for transfusion is gestation as shown in the following graph where the proportion transfused for each gestation falls from 100% at 23/24 weeks to 4% at 30 weeks.
For the babies who were transfused and survived for more than 7 days the following graphs shows the median number of transfusion (with range in brackets) for each gestation.

4.3 Reducing the need for transfusion:

4.3.1 Delayed cord clamping: Waiting for 30 to 120 seconds before clamping the cord allows about 15 to 20 mls/kg of blood to move back from the placenta to the baby. There is evidence from trials to date that this will reduce the need for later blood transfusion (OR 0.61, 0.46-0.81) and reduces the number of transfusions (men diff -1.26, -1.87 to -0.64). The number of very preterm babies in these trials is limited and this question is being addressed in the large multicentre Australian Placental Transfusion Study (APTS).

At RPAH, this intervention will be performed as part of this trial until recruitment concludes.

4.3.2 Limiting blood sampling: blood loss through sampling is one of the main predictors of transfusion needs. Strategies that have been shown to reduce blood testing losses include: admission blood testing from umbilical cord or placental blood; using bedside point of care testing and rationalising the frequency and volume of blood drawn. From December 2016, there will be a new point of care blood gas machine which will also measure electrolytes and bilirubin on micro samples. This may offer opportunities to reduce blood sampling volume.

4.3.3 Erythropoetin: Preterm babies have low erythropoietin levels and exogenous erythropoetin to reduce transfusion need has been the subject of many clinical trials. Systematic review of these trials shows that early (starting before 8 days) or late EPO reduces need for one or more transfusion and the number of transfusions per baby (mean difference, -0.27 and -0.22 of a transfusion for early and late EPO respectively). Early EPO reduces donor exposure but the impact of both strategies on donor exposure is limited by early transfusion prior to trial enrolment. There is a non-significant trend to a higher rate of ROP with early EPO.

At RPAH, it is interpreted that limited impact on number of transfusion and donor exposure does not justify routine use of EPO but it should be considered in selective cases where there is an need to minimise the risk of requiring a transfusion, e.g babies of Jehovah’s Witnesses.

4.4 Transfusion thresholds. There have been four clinical trials of higher vs lower haemoglobin thresholds for transfusion, the largest of which was the multicentre PINT trial. Systematic review of these trials shows no difference in neonatal morbidity and mortality and
no difference in neurodevelopmental outcome at 18-21 months. Lower thresholds lead to a significant reduction in the number of transfusions (mean diff -1.12 transfusions).  

At RPAH, the lack of benefit for a higher threshold indicates that we should be guided lower haemoglobin thresholds as in the table below, which is modified from the PINT trial which enrolled babies less than 31 weeks and less than 1000g.

<table>
<thead>
<tr>
<th>Age</th>
<th>Respiratory Support</th>
<th>No Respiratory Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 days</td>
<td>&lt;105 g/L</td>
<td>&lt;90 g/L</td>
</tr>
<tr>
<td>≥ 15 days</td>
<td>&lt;80 g/L</td>
<td>&lt;70 g/L</td>
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</tbody>
</table>

These thresholds are for guidance only and should be individualised considering the following factors:

- Severity of respiratory disease (and other condition)
- Any symptoms that might relate to anaemia e.g. increasing apnoeas.
- The reticulocyte count.
- Any evidence of on-going blood loss or haemolysis (e.g. a rhesus baby who’d been managed with intra-uterine transfusions).
- Possible or proven sepsis

4.4 Process for Top up Blood Transfusion:

4.4.1 Consent: Informed written consent must be obtained from one of the parents in all but the most critical situations, such as described for acute blood loss above. Use form MR 300: Request/Consent for medical procedure/treatment – Minor.

4.4.2 Specimen collection: Initial group and cross-match will require 1.0ml of blood (into a plain tube) from baby and 10mls of blood from mother. Because all mothers have blood taken for cross match prior to going into labour, the blood bank may well have mother’s blood. Patient details must be hand written on the specimen tube. The specimens should be collected in the presence of a witness who should confirm the identity of the patient against that on the tube and request form and confirm that with a signature.

4.4.3 Request forms: Group and Screen/Cross-match orders are placed on a manual hand written ‘Request for Blood Bank Services’ form. After the first transfusion, blood can be ordered by contacting blood bank on 88033 and confirming they do not need a further specimen for cross match. Orders are collected from blood bank with the ‘RPAH – Blood Product Issue’ pink form.

4.4.4 Blood for top up transfusion should be:

- Leucocyte depleted, CMV negative and irradiated. Irradiation for RPAH now occurs off site so this may lead to a few hours delay in blood being available.
- Infused through a leucocyte filter.
- The volume should be prescribed on the fluid chart to run over four hours. There is no indication for routine frusemide but consider giving 1mg/kg IV at the start of the transfusion if there is risk of fluid overload.
4.4.5 Volume for transfusion: There are two methods for calculating volume for transfusion:

1. A standard volume of 20mls/kg: This will suffice for most top up transfusions in preterm babies.
2. An individualised volume: Based on current and target haemoglobin using the formula:
   \[
   \text{Transfusion Volume (mls)} = \text{Weight (kg)} \times \text{Blood Volume (ml/kg)}^1 \times (\text{desired Hb} - \text{current Hb}) \times \text{Hb of donor blood}^2
   \]
   - Estimated blood volume will range from 100mls/kg in an extremely preterm baby to 80mls/kg in a term baby.
   - Estimated haemoglobin (g/L) of leucocyte depleted donor red cells is approximately 210 g/L

Note that the “Blood and Blood Product Transfusion” sticker shown below should be completed and stuck on the current continuation sheet in the medical record when the blood product transfusion is set up.

5. Complications of red cell transfusion.

Complications of red cell transfusion are rare and most likely to be seen after massive or exchange transfusion but include:

- **Transfusion reactions:** Very unusual in the newborn due to limited ability to generate an allergic response.
- **Immunological complications:** e.g transfusion related lung injury, transfusion associated graft vs host (the reason blood for neonatal transfusion is irradiated).
- **Metabolic complications:** Hypocalcaemia, hypomagnesaemia, hypo or hyperkalaemia, metabolic alkalosis or acidosis, impaired glucose homeostasis and hypothermia (the reason we warm blood in exchange transfusion.
- **Coagulopathy** (as described above) due to inadequate replacement of coagulation factors during massive or exchange transfusion.
- **Infusion complications:** e.g infection, air embolus.
• Transfusion associated NEC (TANEC). Defined as NEC developing within 48 hrs of a blood transfusion. Currently uncertain whether this is association or causation. Meta-analysis of observational studies reports moderate risk of bias and that the reports do not address the fact that there are many cases of NEC that are not associated with transfusion, and many transfusions happen in preterm neonates who are not linked to NEC within 48 hours. Some authors have suggested that withholding feeds around a transfusion may reduce the risk of TANEC. The level of evidence around this is low therefore it is not routine practice at RPAH to withhold feeds during transfusion.

6. Platelet Transfusions for Thrombocytopenia.

Thrombocytopenia in the newborn is usually seen within the first 72 hours after birth, although infection or NEC at any time can cause thrombocytopenia. It not within the scope of this guideline to provide a detailed discussion of the investigation of thrombocytopenia but the following causes should be considered.

- Placental insufficiency, both that causing IUGR and sub-acute perinatal asphyxia.
- Congenital viral and perinatal bacterial infection.
- Massive transfusion, particularly exchange transfusion.
- Alloimmune thrombocytopenia, due to mismatched infant/maternal platelet antigens.
- Autoimmune thrombocytopenia associated with maternal ITP or SLE.
- Congenital, aneuploidies, syndromes (e.g TAR, Kasabach Merrit, Wiskott–Aldrich).

6.1 Thresholds for platelet transfusion: There is limited evidence to guide these thresholds so they are largely consensus based. The following thresholds are derived from Australian Patient Blood Management and other neonatal guidelines:

- Less than $30 \times 10^9$ /L in any baby
- Less than $50 \times 10^9$ /L in any clinically unstable baby, or at risk of bleeding (e.g very preterm baby), any baby about to undergo an invasive procedure or any baby with massive transfusion requirements (See MTP above).
- Higher thresholds to be considered in any baby with evidence of bleeding or clinical evidence of poor haemostasis.

6.2 Request forms: Platelet orders are placed on a manual hand written ‘Request for Blood Bank Services’ form and order are collected from blood bank with the ‘RPAH – Blood Product Issue’ pink form. Platelets are ABO matched to the baby need a ‘group and crossmatch’ specimen if one has not already been sent.

6.3 Platelet volume and infusion rate: Prescribe 15mls/kg to be infused over 60 minutes. Higher volumes may be indicated in babies with very low counts e.g $<10 \times 10^9$ /L, faster infusion may be indicated in babies with ongoing bleeding.

6.4 Special requirements:

- Platelets should not be infused through a central PICC line or an umbilical venous line because of the risk of line associated thrombosis unless there is no other option.
- In severe alloimmune thrombocytopenia (platelet count below thresholds above), babies should be transfused with HPA unmatched platelets. There is no indication to wait for HPA matched platelets. If thrombocytopenia is refractory to unmatched platelet transfusion then consider giving HPA matched platelets after discussion with a haematologist.
7. Fresh Frozen Plasma (FFP) Transfusion for Coagulopathy.

FFP is a source of all clotting factors including V, VIII and Fibrinogen. It may be indicated in clinical situations where there is reduced production or increased losses of clotting factors. Investigation of coagulopathy is not within the brief of this guideline but the following causes should be considered in any baby with deranged clotting studies.

- Heparin contamination of sample if taken from umbilical or peripheral arterial line.
- Asphyxia, particularly if there are clinical pointers to longer standing sub-acute fetal compromise.
- Disseminated intravascular coagulation, usually together with thrombocytopenia in a baby with sepsis.
- Transfusion associated coagulopathy, due to inadequate replacement of clotting factors in a baby needing massive or exchange transfusion.
- Vitamin K deficiency, unlikely if they baby has had intramuscular Vit K prophylaxis.
- Inherited clotting factor deficiencies e.g haemophilia.
- Inherited liver disease e.g neonatal haemochromatosis.

7.1 Threshold for FFP transfusion: An INR ≤ 2.0 should not be associated with an increased risk of serious bleeding. FFP should be considered with an INR > 2.0 depending on the underlying cause and the clinical condition of the baby.

7.2 Request forms:

- FFP is ordered by contacting blood bank on 58033 and is collected from blood bank with the ‘RPAH – Blood Product Issue’ pink form. FFP issued for neonates is usually group AB.
- If Group AB is not available and a ‘group and cross match’ specimen has not been previously sent, then the blood bank may request a specimen depending on the urgency of the clinical situation.

7.3 FFP volume and infusion rate: Prescribe 15mls/kg to be infused over 60 minutes. Faster infusion may be indicated in babies with ongoing bleeding see Massive Transfusion Protocol above.
Key Points

<table>
<thead>
<tr>
<th>Key Point</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Consider acute perinatal blood loss at resuscitation if there is a history of APH and the baby remains pale. Other signs may include tachycardia and weak heart sounds.</td>
<td>Clinical experience</td>
</tr>
<tr>
<td>If continuing blood loss requires transfusion of more than 40mls/kg then initiate the massive transfusion protocol.</td>
<td>Level of evidence IV&lt;sup&gt;1,2&lt;/sup&gt; Recommendation strength C</td>
</tr>
<tr>
<td>Delaying clamping of the umbilical cord for between 30 and 120 seconds reduces need for later transfusion in preterm babies.</td>
<td>Level of evidence I&lt;sup&gt;3&lt;/sup&gt; Recommendation TBA at conclusion of APTS trial.</td>
</tr>
<tr>
<td>There is no difference in outcomes between preterm babies randomised to lower vs higher haemoglobin transfusion thresholds. Top up transfusions should be considered at lower thresholds.</td>
<td>Level of evidence I&lt;sup&gt;4,5&lt;/sup&gt; Recommendation B</td>
</tr>
<tr>
<td>Platelet transfusion should be considered in any baby with a platelet count of $&lt; 30 \times 10^9$ and in any unstable baby with platelet count $&lt; 50 \times 10^9$.</td>
<td>Level of evidence IV&lt;sup&gt;6&lt;/sup&gt; Recommendation strength C</td>
</tr>
<tr>
<td>An INR $\leq 2.0$ should not be associated with an increased risk of bleeding. Consider FFP transfusion in babies with an INR $&gt; 2.0$ depending on the clinical condition of the baby.</td>
<td>Level of evidence IV&lt;sup&gt;7&lt;/sup&gt; Recommendation strength C</td>
</tr>
</tbody>
</table>

References


Minimum list (nothing to do with transfusions).

- Legislative Compliance: Organisation, Management and Staff Obligations – Governing Body and Management manual, Policy Number 2.7.1
- Code of Conduct – Governing Body and Management Manual, Policy Number 1.1