June 2007 Volume 100 Number 6

IRISH MEDICAL ORGANISATION
Ceardchumann Dochtúirí na hÉireann

IMJ
Official Journal of the
Irish Medical Organisation

Irish Medical Journal Supplement — Established 1867

Transfusion of Blood Components to Infants under Four Months:

Review and Guidelines

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See Appendix 2*

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Summary of the National Blood Users Group guideline for the transfusion of blood components to preterm infants

This review was undertaken by the National Blood Users Group (NBUG) to provide evidence based guidelines for the provision of blood component therapy for infants under four months. Blood transfusion support is an integral part of the neonatal intensive care provided to preterm infants. In current practice most transfusions in infants involve small volume, so-called, 'top-up' red blood cell (RBC) transfusions given to the preterm infant. Infants are the longest living survivors of blood transfusion and are the patient group most at risk for the long-term consequences of transfusion transmitted infections (see section 2). Every effort has to be made to reduce transfusions and donor exposure in this most vulnerable group of transfusion recipients.

Small volume red blood cell transfusion of preterm infants

There is abundant evidence that Neonatal Intensive Care Units (NICUs) that use transfusion guidelines prescribe less transfusions.

- All NICUs should have written, consensus based guidelines that underline transfusion policy. Guidelines should be regularly updated in-line with the best available evidence and their implementation should be regularly assessed by audit (Sections 3 and 4).

Although most preterm infants with birth weight of less than 1000g will require RBC transfusion, the majority of infants with birth weight greater than 1500g do not require RBC transfusion.

- All NICUs should audit RBC transfusion practice, stratified by birth weight, at least annually and should use their audit result as a benchmark for comparison with practice nationally and internationally.

Minimising donor exposure is important in reducing the risk of transfusion-transmitted infections.

- Any infant who is likely to require recurrent RBC transfusion should have a Pedipack (a unit of packed red blood cells divided into multiple units) assigned to them as soon as a decision to transfuse has been made. The donor exposure of infants should be regularly audited (Section 6.3).

Blood loss as a result of repeated phlebotomy is an important contributory cause of the anaemia of prematurity requiring transfusion support in the low birth weight infant undergoing intensive care.

- Neonatal units should liaise closely with laboratory experts to minimise the amount of blood drawn for testing (Section 5.1). Laboratories may need to up-date their equipment to minimise losses.
- Regular training of all staff undertaking phlebotomy in infants is essential.
- The recommendations of the Neonatal Intensive Care Outcomes Research and Evaluation (NICORE), Ireland, to restrict phlebotomy losses should be implemented. NICORE provides 'audit tools' to audit the effectiveness of measures in reducing blood losses (Section 5.1).

Erythropoietin (EPO). EPO cannot currently be recommended. While meta-analyses of controlled clinical trials show that EPO given with iron reduces RBC transfusions in preterm infants, the clinical benefit is limited. The very low birth weight infants with the highest transfusion requirements (and phlebotomy losses) in the first 2-3 weeks of life are slow to respond. Furthermore, the recent Cochrane Database meta-analysis (2006) showed an increased risk of retinopathy of prematurity with early EPO treatment (Section 5.4).

Exchange transfusion in a neonate constitutes a massive transfusion involving the replacement of one or two blood volumes. Exchange transfusion is now an infrequently performed procedure with significant risks and should only be undertaken by trained medical personnel in a NICU with full monitoring and resuscitation capabilities and may be an indication for tertiary referral (Sections 7.3, 7.3.1 and 7.3.2).

Platelet transfusion

Platelet transfusion guidance in preterm infants lacks a strong evidence base (Section 8.1 and 8.2).

- NICUs should produce a consensus guideline which should be the subject of regular audit.

Neonatal allo-immune thrombocytopenia (NAIT) should always be considered when an isolated severe thrombocytopenia is detected in an otherwise healthy child at birth and should also be included in the differential diagnosis of thrombocytopenia in the sick infant (Section 8.5.1).

- Treatment with platelet transfusion should not be delayed pending the results of investigations.
- Human Platelet Antigen (HPA) 1a and 5b negative platelets which are compatible in 95% of cases of NAIT should be provided for transfusion in all cases of severe thrombocytopenia where NAIT is suspected.
- Transfusion of random donor platelets is an appropriate strategy in the management of NAIT if compatible platelets are not available.

FFP/SD-Plasma

To reduce the risk of transfusion transmitted vCJD, single donor Irish fresh frozen plasma (FFP) has been replaced by the Irish Blood Transfusion Service with pooled, solvent detergent (SD) treated, US sourced, plasma (SD-Plasma). The indications for FFP and SD-Plasma are the same (Section 10.1).

- Routine administration of FFP/SD-Plasma to prevent periventricular haemorrhage in preterm infants is not indicated
- FFP/SD-Plasma should never be used as a simple volume replacement in babies.
- FFP/SD-Plasma use should be regularly audited.

We recommended that all NICUs should have access to a Consultant Haematologist whose responsibilities includes oversight of laboratory technology to minimise phlebotomy losses and the regular audit of RBC, platelet and FFP/SD-Plasma usage.

Neonatal and Fetal Transfusion

Section 1 Introduction

Blood transfusion therapy is an integral part of modern neonatal care. Preterm infants are one of the most heavily transfused

groups of patients with the greatest potential for longevity.[1]
Transfusion practices vary among neonatologists, largely due to a lack of evidence upon which to base practice.[2]
Most RBC transfusions are small volume and are administered in the first month of life to preterm infants with a birth weight less than 1kg,[3] primarily for anaemia secondary to phlebotomy losses and cardiorespiratory instability.[4]
We have reviewed the current evidence base for neonatal transfusion practice including published guidelines in this area and have endeavoured to arrive where possible at a consensus approach to optimal management of transfusion in these infants.

1.1 Anaemia in preterm infants

The mean blood volume of the term infant is 85 ml/kg and that of the preterm is slightly higher.[5] During the first weeks of life, all infants experience a decline in circulating red blood cell volume as a result of physiological factors. In healthy newborns, the physiological decline in circulating red cell volume reaches a Haemoglobin (Hb) nadir of about 9 to 12g/dl at an age of 10 to 12 weeks of age; this is known as the 'physiological anaemia of infancy'.
In preterm infants, this decline occurs at an earlier age and is more severe, with a Hb nadir of 8g/dl for infants with birth weights of 1.0 to 1.5kg and 7g/dl for those less than 1 kg. The causes of this anaemia are multifactorial but include phlebotomy losses and a relatively diminished erythropoietin (EPO) secretion in response to anaemia. One possible mechanism for this blunted EPO response is that the major site of erythropoietin synthesis in utero is in the liver which is much less sensitive to tissue hypoxia than the kidney.[6] The switch from liver to kidney as the predominant site of EPO synthesis is set at conception and does not appear to be accelerated by preterm birth.[7] Increased clearance of plasma EPO in infants may also contribute to low plasma EPO levels.[8] In addition, infants delivered before 28 weeks of gestation (birth weight < 1.0 kg) are born before the bulk of iron transport through the placenta from mother to fetus has occurred.[7] The predominant haemoglobin in preterm infants is fetal haemoglobin (HbF), which is relatively poor at oxygen delivery to the tissues. When preterm infants are transfused with adult blood containing haemoglobin A, the shift of the oxygen dissociation curve as a result of the presence of haemoglobin A facilitates delivery of oxygen to the tissues.[9] Accordingly, the definition of anaemia and the need for transfusion in premature infants must be based not only on the haemoglobin level but also on oxygen requirements and the ability of an infant's circulating haemoglobin to release oxygen.[9] Hence preterm infants of very low birth weight enter extrauterine life with low iron stores, a small circulating red cell mass and encumbered by Hb F to deliver oxygen to the tissues.

1.2 Changing transfusion patterns

Over the last ten years, there has been a progressive decline in the number of RBC transfusions given to preterm infants. This is due to a number of factors including improved prevention and treatment of respiratory distress syndrome with surfactant, assisted ventilation, inhalation of nitric oxide and the reduction of blood loss for analytical purposes.[10] A major factor has been the implementation of more restrictive guidelines for transfusions due to an increasing awareness of the risks of blood transfusions.[3,11,12]
Widness et al, showed that the proportion of infants with birth weights from 1.0-1.5kg who received no transfusions increased from 17% in 1982 to 30% in 1989 to 64% in 1993.[3]

Section 2 Risks of transfusion in neonates

2.1 Transfusion transmitted Infections

2.1.1 Known viruses

Because of their long life expectancy and relatively immature immune system, transfusion transmitted diseases in infants can have serious consequences. Current blood donor selection procedures and testing using serological immunoassays and nucleic amplification testing (NAT) for HCV and HIV-1 have reduced the residual risk of transfusion transmitted HIV and HCV to an estimated 1 in 4 million per units transfused. Risk estimates for hepatitis B virus (HBV) are the most difficult to calculate because of the transient nature of HBV in adults, but a conservative estimate is of the order of 1 in 200,000 per unit transfused. Whilst 95% of immunocompetent adults will clear HBV infection, a newborn infected with HBV almost invariably becomes a carrier.

2.1.2 Variant (v)CJD

vCJD, a fatal disease, for which there is no treatment, must now be considered a transfusion transmissible disease, following reports of transmissions in the UK from donors who, subsequent to donation, went on to develop vCJD.[13,14] Although the actual risk of transfusion transmitted vCJD may be low in Irish transfusion recipients, the recent diagnosis of vCJD in an Irish donor subsequent to donation means that, in the absence of a blood screening test, transmission remains a possibility for transfusion recipients.

Rodent experimental models of Transmissible Spongiform Encephalopathies suggest that most infectivity in blood resides in the buffy coat and plasma.
A number of measures have been introduced by the Irish Blood Transfusion Service (IBTS) to protect the Irish blood supply including:

- The leucocyte reduction of blood components.
- The exclusion of donors who have spent extended periods of time in the UK during the BSE epidemic (1980-1996).
- The exclusion of donors who have themselves been transfused.
- The replacement of single donor Irish fresh frozen plasma (FFP) with pooled solvent detergent (SD) treated, US sourced, plasma (so-called SD-Plasma). Solvent detergent treatment effectively eliminates the risk of HBV, HCV and HIV because they are enveloped viruses; however the process has no effect on non-enveloped viruses such as Hepatitis A and Parvovirus. Although the manufacturer takes measures to reduce the risk of transmission of these small non-enveloped viruses in SD-Plasma, the risk has not been eliminated because these are pooled blood products.
- The use of prion removal filters for red blood cells is currently being evaluated by the IBTS.

2.1.3 Cytomegalovirus (CMV)

Early studies in the 1970's and 80s showed a significant risk of transfusion transmitted (TT)-CMV infection in the preterm infant particularly those born to seronegative mothers. A marked reduction in the incidence was demonstrated through the exclusive use of CMV-seronegative blood for transfusion.[15,16]
CMV is highly cell-associated and latently infected monocytes are thought to be the primary vectors for TT-CMV. The two methods used to prevent TT-CMV are the use of blood from donors who are negative for CMV antibodies and the use of units that have been filtered to remove white blood cells including those harbouring latent CMV (leucoreduction). Neither method provides absolute protection from TT-CMV in the allogeneic stem cell transplant setting.[17] The Council of Europe[18] and the American Association of Blood Banks[19] affirm the equivalence of seronegative and leucoreduced units for the purpose of prevention of TT-CMV. Controversy still exists. A Canadian consensus conference in 2000 addressed the issue as to whether CMV serological testing could be abandoned by blood transfusion services which had implemented universal leucoreduction of

blood components.[20] The majority opinion recommended the continued provision of both leucoreduced and CMV-seronegative blood components for patients at greatest risk of TT-CMV, namely CMV-seronegative allogeneic stem cell recipients, the fetus, and CMV-seronegative pregnant women, but did not recommend serological testing in addition to leucoreduction for neonates.[20] In a systematic review of the literature aimed at determining the effectiveness of red cell leucocyte reduction on CMV-transmission risk in neonates, only two studies were deemed evaluable by the authors.[21] The pooled OR was 0.19 (95% CI, 0.01-3.41), suggesting a clinical, but nonsignificant benefit of leucocyte depletion; however further research was needed to elucidate the effect of leucoreuction on TT-CMV infection in neonates.[21] At present all blood components issued for neonatal use by the IBTS are both leucocyte-reduced and from CMV-seronegative donors. However, in an emergency, or where Human Platelet Antigen (HPA) or Human Leucocyte Antigen (HLA) matched platelets are required, and CMV-seronegative blood components are not available, the transfusion of leucoreduced components that have been tested to ensure a residual leucocyte count of $< 1x10^6$ is acceptable *(level IIb evidence, grade B recommendation)*.

2.1.4 Bacterial contamination

There is a small but potentially fatal risk of bacterial infection of the order of 1 in 8-13 million for red cell units but of a much higher magnitude (1 in 270,000-300,000 per platelet dose) for platelets because they are stored at room temperature.[22-27] The IBTS has introduced the routine bacteriological screening of platelets to reduce this risk.

2.2 Retinopathy of prematurity and bronchopulmunary dysplasia

A potential role for blood transfusions and /or anaemia in the pathogenesis of retinopathy of prematurity (ROP) has been suggested.[28,29] However a number of prospective, randomised, trials have failed to show a link between ROP and anaemia or transfusions[30-32] (see also section 5.4 on erythropoietin).

At least one study has demonstrated an association between the number of packed red blood cell transfusions given in the first eight 8 days of life and the subsequent development of chronic lung disease (CLD), bronchopulmonary dysplasia.[33] However another study has shown no increase in oxygen free radical generation in preterm infants who developed CLD[34] and restrictive versus liberal transfusion thresholds had no effect on incidence of CLD in preterm infants in two randomised trials.[31,32]

Section 3 Evidence of benefit of transfusions

Objective evidence of benefit from transfusions through randomised control trials is scanty. Traditional criteria of 'symptomatic' anaemia in preterm infants include pallor, tachycardia, apnoea, poor feeding and weight gain.[35] A number of authors have tried to demonstrate objective evidence of benefit from transfusion, such as decrease in apnoea, heart rate and improved systemic oxygen transport. Findings have not consistently shown benefit from transfusion. However, most studies included stable infants with relatively high pretransfusion haematocrits and small volumes of blood were transfused.[36-44] A recent small (n=32) study showed that apparently 'stable' anaemic infants may be in a clinically unrecognised high cardiac output state.[45] Infants were grouped prospectively according to pretransfusion haematocrit ranges for cardiac function analysis: </- 21% (low), 22% to 26% (mid), and > 27% (high). Before transfusion, the low- and mid-range groups had higher left ventricular end systolic and diastolic diameters, in comparison with the high range group. The low range group had increased stroke volume in comparison with the high range group. Some echocardiographic measurements did not improve within 48 hours after transfusion.[45]

Few studies have examined the effects of transfusions administered to critically ill infants in the first weeks of life. The physiologic impact of anaemia is altered by so many variables that it is difficult to find simple clinical or laboratory indications to determine when intervention is required. Measurement of tissue oxygenation using whole blood lactate concentration or fractional oxygen extraction may be a better marker of transfusion need than the haemoglobin level,[46,47] but clinically applicable measurement techniques are currently not readily available.

The recent 'Premature Infants in Need of Transfusion (PINT)' study reviewed the effect of withholding transfusion until very stringent criteria were met.[31] This multicentre, randomised, trial was conducted in 10 neonatal intensive care units in 3 countries to determine whether transfusion triggered by low vs. high haemoglobin concentration affects mortality or severe morbidity in extremely low birth weight (ELBW) infants (< 1000g birth weight). Eligible infants < 48 hrs of age, recruited over 24 months, were randomised to an algorithm of low or high Hb triggers adjusted for cardiorespiratory disease and falling with postnatal age (max Hb 13.5g/dl, min 7.5 g/dl, differing by 1-2 g/dl depending on age and respiratory support, and maintained until discharge).

451 infants were randomised, 223 in the low Hb and 228 in the high Hb group. Groups were similar, with mean birth weight of 770g and gestational age of 26 weeks. Emergency transfusions were permitted for shock, sepsis, and surgery. Fewer infants received one or more transfusions in the low threshold Hb group (89% low versus 95% high, P = .037). The low threshold group received fewer RBC transfusions (mean, 4.9 units) than the high threshold group (mean, 5.7 units) but the difference did not reach statistical significance (P =.070). The mean number of blood product donors to which infants were exposed was slightly lower in the low threshold group for all blood products but was only statistically significant for RBC donors; 2.1 versus 2.6, P =.035.

There was no difference in major morbidity or mortality between both groups, (as measured by death before discharge, bronchopulmonary dysplasia, retinopathy of prematurity, or brain injury).

Table 1 PINT Study [31]

	Hb Threshold: allocation group		
Outcome	Low Hb N = 223(%)	High Hb N= 228 (%)	OR 95% CI
Death before discharge	48/223 (21.5)	40/228 (17.5)	1.38 (0.84, 2.27)
Bronchopulmonary Dysplasia (BPD)	101/175 (57.7)	103/188 (54.8)	1.18 (0.76, 1.85)
Retinopathy of Prematurity (ROP) grades 3 to 5	33/175 (18.9)	33/188 (17.6)	1.27 (0.71, 2.26)
Ultrasound Brain Injury	40/216 (19)	45/217 (21)	0.8 (0.5, 1.4)
Death or Severe Morbidity	165/223 (74)	159 /228 (69.7)	1.30 (0.83, 2.02)

With the exception of brain injury, the composite and individual outcomes each slightly favoured the high threshold group, but all differences were statistically non-significant (Table 1). There were no statistically significant differences between groups in any

secondary outcome e.g. growth, apnoea etc. The high threshold group had a mean Hb concentration of about 1g/dl higher than the low threshold group during the first 4 weeks of life and the authors concluded that maintaining a higher Hb level in ELBW infants confers little evidence of benefit.[31]
A recent smaller, single-centre (Iowa Trial), randomized clinical trial of restrictive versus liberal transfusion triggers suggests a careful re-examination of restrictive RBC-transfusion practice may be required.[32] 100 hospitalised preterm infants were assigned randomly to either a liberal or restrictive transfusion group. In each group, the transfusion threshold levels decreased with improving clinical status, measured by the need for respiratory support. Tracheally intubated for assisted ventilation (phase 1) infants in the liberal and restrictive transfusion groups received an RBC transfusion if their haematocrit levels fell to < 46% and <34%, respectively. While receiving nasal continuous positive airway pressure or supplemental oxygen (phase 2), their hematocrit levels were kept at >38% and >28%, respectively, and if requiring neither positive pressure nor oxygen (phase 3), they were kept at > 30% and >22%, respectively.

The mean birth weight of the liberal-transfusion group was 954g and 958g in the restrictive-transfusion group and mean gestational age for both groups was 28 weeks. Both transfusion programmes were well tolerated. The mean number of RBC transfusions was significantly higher in the liberal group 5.2 compared to 3.3 in the restrictive group but there was a lack of difference in the number of donor exposures which was attributed to the use of a single-donor transfusion programme. The number of infants who required no transfusions was similar at 10% and 12% in the restrictive and liberal groups respectively. There was no difference in survival or in the risk of patent ductus arteriosus, retinopathy of prematurity, or bronchopulmonary dysplasia. No difference was found in the risk of germinal matrix or intraventricular haemorrhage of all grades. The restrictive-transfusion group had more infants with grade 4 haemorrhage, i.e., parenchymal brain haemorrhage (4 vs 0; p=.054) and had more infants with periventricular leukomalacia (4 vs 0), although this difference was not statistically significant (p=.115). Infants in the restrictive-transfusion group had significantly more apnoea than did those in the liberal transfusion group (median: 0.84 vs 0.43 episodes per day; p=0.004) and a significant decrease in the frequency of apnoea after RBC transfusion. The authors suggest that decreased oxygen delivery to the brain may be the mechanism for the increased frequency of brain injury and the more frequent apnoea in infants in the restrictive transfusion group. The increase in severe brain haemorrhage in the restrictive-transfusion group may have resulted from increased cerebral blood flow in partial compensation for the decreased arterial oxygen content in this group.[32]

Bell has provided a useful overview and comparison of these two important studies in the commentary to the PINT Trial.[48] The transfusion thresholds used for the restrictive transfusion groups were similar in the two trials. However, the transfusion thresholds for the liberal transfusion group were higher in the Iowa Trial. As a result, the separation achieved in mean Hb between the two study groups at 4 to 6 weeks of age was 2.5 times larger in the Iowa Trial, 2.7g/dl compared with 1.1g/dl in the PINT Trial.[48] It is possible that the increase in apnoea and brain injury seen in the Iowa Trial resulted from bias or random statistical error, particularly as the composite outcome of parenchymal brain haemorrhage or periventricular haemorrhage was not planned initially as part of the data analysis but was added after the study was completed when the clustering of both single events in the restrictive transfusion group was noted.[48] The second possible explanation noted by Bell is that the higher Hb concentrations maintained in the Iowa Trial liberal transfusion group compared with the corresponding group in the PINT Trial may have conferred protection against apnoea and brain injury.[48] Both studies have shown that restrictive transfusion practice will reduce the number of transfusions to infants but do not necessarily reduce overall donor exposure.[31,32] Bell concludes that 'the drive to eliminate transfusions by tolerating moderate to severe iatrogenic anaemia should be halted until more information is available'.[48]
The PINT Trial group has recently reported preliminary data (published in abstract form) on neurodevelopmental outcome at 18 months.[49] Whilst the authors conclude that maintaining the haemoglobin of extremely low birth weight (ELBW) infants at low rather than high levels does not result in significant differences in survival or neurodevelopmental outcome at 18 months, there is a trend towards better outcome in the high Hb group both in terms primary composite outcome (death, cerebral palsy, blindness, deafness, cognitive delay: 94/208(45.2%) versus 82/213(38.5%), OR (95%CIs) 1.45 (0.94,2.21) P =0.091, and in particular cognitive delay: 38/156 (24.4%) in low Hb threshold group versus 29/165(17.6%), OR 1.75 (0.98,3.11) P =0 .06 in high Hb group.[49]
It is clear neonatologists will have to review this literature carefully in order to formulate transfusion guidelines for their unit.

Section 4 Guidelines for RBC Transfusion

The US Guidelines for Blood Utilisation Review[50]state that 'transfusion practice guidelines are not intended to serve as medical indications for transfusion. Rather, they list clinical circumstances in which transfusions might be administered without additional justification. They include conditions for which transfusion is usually considered reasonable, not mandatory, practice. Not all patients who are considered eligible for transfusion by the guidelines will actually benefit from blood administration. In addition, transfusion may be indicated in clinical situations not falling within the guidelines.' This advice is particularly true for neonatal transfusions as all guidelines currently available are based, predominantly, on expert opinion, in the absence of good evidence for optimal transfusion administration. Many of the guidelines, including these in this document have been reached by consensus or broad agreement and accepted as a standard of care in the absence of clear evidence of benefit of RBC transfusion.

4.1 Selected guidelines from the U.K. and U.S.A.

Table 2. The British Committee for Standards in Haematology Transfusion Task Force, (BCSH) 2004, has issued the following suggested transfusion thresholds for infants under 4 monthsof age[51].

Transfusion of red blood cells	
Anaemia in first 24 hours	Hb 12 g/dl (Hct c. 0.36)
Cumulative blood loss in 1 week in a neonate requiring intensive care	10% blood volume
Neonate receiving intensive care	Hb 12 g/dl
Acute blood loss	10%
Chronic oxygen dependency	Hb 11 g/dl
Late anaemia, stable infant	Hb 7 g/dl

4.2 Table 3. The guidelines from Roseff et al (USA, 2002) are more prescriptive.[1]

Guidelines for transfusion of RBCs in patients less than four months of age.

1. Hct <20% with low reticulocyte count and symptoms of anemia.*
2. Hct <30% with an infant:
   On <35% hood O_2
   On O_2 by nasal cannula
   On continuous positive airway pressure and/or intermittent mandatory ventilation with mechanical ventilation with mean airway pressure <6 cm H_2O
   With *significant* apnea or bradycardia †
   With *significant* tachycardia or tachypnea ‡
   With low weight gain §
3. Hct <35% with an infant:
   On >35% hood O_2
   On continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥6-8cm H_2O
4. Hct <45% with an infant:
   On ECMO
   With congenital cyanotic heart disease

* Tachycardia, tachypnoea, poor feeding.
† More than six episodes in 12 hr or two episodes in 24 hr requiring bag and mask ventilation while receiving therapeutic doses of methylxanthines.
‡ Heart rate >180 beats/min for 24 hr; respiratory rate >80 breaths/min for24 hr.
§ Gain of <10 g/day observed over 4 days while receiving ≥100 kcal/kg/day.

4.3 NBUG Guidelines

Each neonatal department should have transfusion guidelines in place. Guidelines can reduce the number of RBC transfusions to VLBW infants, partly by removing the discretionary element of RBC transfusions.[3,11,12] Clinicians who follow agreed guidelines will give fewer transfusions.

Guidelines for blood transfusion therapy and periodic audit of their implementation should be standard practice in all neonatal units *(level I b evidence, grade A recommendation).*

Reasons for transfusion and perceived benefits or adverse effects must be documented.
The decision to transfuse must be discussed with the baby's parents.

The majority of transfusions are given to infants with birth weight of less than one kilogram. Thus all infants in this group, or any other infant who is likely to require recurrent transfusion should have a Pedipack (a unit of packed red blood cells divided into multiple packs) assigned to them as soon as a decision to transfuse has been made *(level I b evidence, grade A recommendation).*

Volume of blood transfused should be 10-20 mls per kilogram over 2-4 hours (see section 5.2).

Routine replacement of blood loss by phlebotomy is not recommended.

As evidence for when to transfuse is limited, it is not possible to suggest very prescriptive guidelines. Important factors that influence the decision to transfuse include:

- The degree of prematurity. Although most infants weighing more than 1500 g will not require transfusion, the majority of infants weighing less than 1000 g will have a transfusion requirement.[52]
- The degree of illness*
- The postnatal age*

*Younger and more severely ill infants are more likely to require transfusion than older infants who are stable.

Table 4 The following suggested Hb thresholds for small-volume RBC transfusions for neonates are consistent with current expert opinion: *(level IV evidence, grade C recommendation)*

Hb	12-13.0 g/dl with severe cardiopulmonary disease
Hb	10.0-11.0 g/dl with moderate cardiopulmonary disease
Hb	8.0-10.0 g/dl with symptomatic anaemia
Hb	7-8 g/dl late anaemia, stable patient
Hb	10.0g /dl with major surgery

Definitive studies are not available to establish the optimal Hb level for neonates facing major surgery. However, it seems reasonable to maintain the Hb level above 10.0g/dl because of limited ability of the neonate's heart, lungs and vasculature to compensate for anaemia.[53] Additional factors include the inferior offloading of oxygen as a result of fetal Hb and the developmental impairment of neonatal renal, hepatic and neurological function.[53] This transfusion guideline should be applied with flexibility to individual infants facing surgical procedures of varying complexity.[53]

4.4 Acute blood loss

Acute life-threatening haemorrhage in the newborn is rare. Causes include acute feto-maternal transfusion, twin-twin transfusion, bleeding from a vasa praevia or birth injury. Restoration of intravascular volume with crystalloid and/or colloid solutions is a first priority. Group O, Rh D negative, plasma reduced, CPDA-1, RBCs less than 5 days old, should be immediately transfused in an acute resuscitation. When possible, use of a blood warmer is recommended for rapid or massive transfusion (>25 ml/kg). A thermostatically controlled device manufactured and approved for blood warming is recommended. Liver and renal function immaturity renders infants vulnerable to metabolic imbalance e.g. hypocalcaemia from massive transfusion and careful monitoring is required (see section 7.3.1: risks of exchange transfusion). Dilutional haemostatic disorder can occur in any massive transfusion setting and is characterised by thrombocytopenia, hypofibrinogenaemia, and prolongation of both the prothrombin time and partial thromboplastin time; fibrin degradation products and/or fibrin D-dimers are often present.[52] A severe coagulopathy with disseminated intravascular coagulation (DIC) may arise. Clinically, the patient may present with microvascular bleeding or oozing from sites of injury, venipuncture sites, and mucosal surfaces. The potential for dilutional / consumptive haemostatic disorder in any massive transfusion setting requires laboratory assessment for abnormal coagulation tests and thrombocytopenia and treatment with plasma and platelets.[52] The neonatal liver is less able to correct for hypofibrinogenaemia than the adult liver and cryoprecipitate may be required (see section 11 on cryoprecipitate).

If CPDA-1 RBCs are not available, red cells in additive solution (SAG-M), ≤ 5 days old, are suitable; the critical issue is the age of red cells, as hyperkalaemia increases with the shelf-life of the component and is a risk with older blood when rapidly transfused. Clinicians should also be aware that SAG-M blood contains virtually no coagulation factors and FFP (or SD-Plasma) may be required for the reasons outlined above (see section 6.2: RBC anticoagulant/preservative solutions).

Section 5 Methods of Diminishing Need for Transfusion

5.1 Reducing iatrogenic blood loss

There is a highly significant correlation between blood loss from sampling and transfused blood volume; the highest frequencies of sampling occurring during the first week of life, in very preterm infants and in critically ill infants.[54]
The number of blood samples taken and the amount of blood taken during blood sampling should be kept at a minimum.[55]
As technology improves smaller and smaller volumes of blood are required for analysis. A recent randomized, controlled trial documented significant reductions in neonatal RBC transfusions with the use of an umbilical artery catheter with an in-line blood gas and chemistry monitor.[56]
The recent recommendations of Neonatal Intensive Care Outcomes Research and Evaluation (NICORE) Ireland to restrict phlebotomy losses should be implemented[57] *(Grade A Recommendation) :*

- Minimisation of blood volumes required by liaison with laboratory colleagues and effective use of technology
- Regular training of all staff undertaking phlebotomy
- Regular audit of effectiveness in reducing blood losses. 'Audit tools' are provided by NICORE[57]

5.2 Dose (volume) of RBCs

The optimum volume of RBCs to be transfused in the small volume, top-up setting has not been established. One study randomised preterm infants to receive 10 or 20 ml/kg RBCs; the larger volume produced greater rises in Hb without any detrimental effects on pulmonary function.[58] When a transfusion is indicated, the larger volume could lead to a reduction in transfusion requirement and possibly a reduction in donor exposure.[57,59]

5.3 Autologous transfusion in an infant can occur by delaying cord clamping or collecting, storing and reinfusing cord blood.

5.3.1 Delayed cord clamping

Usher et al, in 1963 demonstrated, by measuring blood volume of newborns, that term infants with delayed cord clamping had a blood volume of 126 ml per kg at 5 minutes of age and 93 ml per kg at 72 hours of age.[60] Corresponding values in infants with immediate cord clamping (usually within 10 seconds of birth) were 78 ml per kg at birth and 82 ml per kg at 72 hours of age. Other studies have indicated that babies with delayed cord clamping and with higher blood volumes have less respiratory distress syndrome and require less packed cell transfusions[61] but some investigators showed no advantage to the infant.[62]

A randomized study in very low birth weight preterm infants delivered by Caesarean section found a decrease in the transfusion requirement in infants randomised to a 45 second vs 20 second cord clamp time.[63] Circulating RBC volume measured directly with biotinylated RBCs significantly increased in preterm infants after delayed versus immediate cord clamping.[64,65] A 2004 meta-analysis of randomised, controlled trials on early versus delayed cord clamping (DCC) in preterm infants showed that DCC was associated with fewer transfusions for anaemia or low blood pressure than early clamping, most outcomes however, even when taking all trials together, had wide confidence intervals, so the results should be interpreted with caution.[66] This Cochrane review also noted a decrease in overall IVH, but no differences were found for severe IVH.[66] A subsequent randomised controlled trial of immediate (5-10 secs) versus delayed (30-45 secs) cord clamping and lowering of the infant below the level of the placenta in VLBW infants showed significantly less IVH, grades 1 and 2, (but not severe IVH, which was rare) and late-onset sepsis in the DCC group, especially in male infants.[67] The authors speculate that the protective effect on late sepsis could be attributed to the high concentration of primitive haematopoietic progenitor cells present in high concentration in extremely preterm infants.[67] The accompanying commentary to this article notes that the study did not document that a placental transfusion had actually occurred in the DCC group and that placental transfusion may be influenced greatly by respiration, so that timing of cord clamping alone may not be enough.[68] The editorial suggests that as there does not seem to be disadvantages to DCC, cord clamping should be deferred for a short time.[68] Even among term infants the practice of delayed cord clamping appears to be safe.[69] The clinical benefits of increasing RBC volume in premature infants by delaying cord clamping requires further investigation. Cord-clamping practice guidelines for obstetricians and paediatricians are required.[66-70]

5.3.2 Cord Blood Collection

The potential for bacterial contamination limits the widespread adoption of the collection of cord blood as a source of autologous RBCs for transfusion to preterm infants.[71] With meticulous preparation, the technique has been applied successfully with reduction in allogeneic donor exposure.[72]

5.4 Erythropoietin

Low plasma EPO levels provide a theoretical rationale for use of EPO therapy in the prevention or treatment of anaemia of prematurity. The primary goal of EPO therapy is to reduce transfusions. Recombinant human erythropoietin (rHuEPO) is known to be effective in increasing red blood cell production in newborn infants with increased reticulocyte counts and iron utilisation. Newborn infants have a larger volume of distribution and a more rapid elimination of erythropoietin, necessitating a higher per kilogram dosage.[73] The efficacy of rHuEPO in reducing blood transfusions in the anaemia of prematurity has been systematically reviewed (Vamvakas 2001,[74] Garcia 2002,[75] Kotto-Kome 2004,[76] Cochrane Database, 2006[77-79]). Vamvakas et al concluded that the studies differed markedly from one another in multiple ways producing widely variable results that could not be explained; hence firm recommendations could not be made. Garcia et al concluded that administering rHuEPO to VLBW neonates can result in a modest reduction in late RBC transfusions and that the effect is dependent on the dose of rHuEPO used. Kotto-Kome et al concluded that if EPO is started in the first week of life, a moderate reduction can be expected in the proportion of VLBW neonates transfused; the reduction being less significant for 'early' transfusion than for 'late' transfusion. Franz et al have demonstrated that in the presence of restrictive guidelines for blood transfusion, the number of red blood cell transfusions and volume transfused was not influenced by the administration of rHuEPO.[12]

Side effects of rHuEPO noted in early studies include the rare report of sudden infant death syndrome and the more common induction of iron deficiency. Thus treatment with erythropoietin must be accompanied by administration of iron daily. Oral and intravenous iron are known to produce oxidative stress. A possible increase in prevalence of retinopathy of prematurity (ROP) has been described in infants given rHuEPO as compared to matched controls.[80] Transient neutropenia has been noted in some trials but has not been noted in recent studies.[81] No adverse effect on neuro-developmental outcome for very low birth infants has been demonstrated [82]

Three recent systematic reviews (Cochrane Database, 2006) of the role of erythropoietin for preventing red blood cell transfusion

in preterm infants and/or low birth weight infants have been performed :

1. The early administration of EPO (starting in infants ≤ 7 days of age) vs placebo/no treatment concluded that the significant reductions in RBC transfusions and donor exposure detected were small and of limited clinical significance; however there was a significant increase in the risk of stage ≥ 3 ROP in the RHuEPO group.[77] The use of EPO in combination with dedicated red blood cell transfusion units did not significantly reduce the use of one or more red blood cell transfusions. Due to the limited benefits and the increased risk of ROP, early administration of EPO is not recommended and efforts should focus on limiting donor exposure through satellite units, on the development of practice guidelines to limit blood losses as the need for RBC transfusions is linked to the loss of blood from sampling for laboratory testing.[77]

2. Meta-analysis of late EPO (starting in infants > 7 days of age) vs placebo/no treatment showed significant reduction in RBC transfusion which were deemed to be of marginal clinical importance.[78] Late EPO did not increase risk of ROP.

3. Early vs late EPO: early EPO administration resulted in a non-significant reduction in the use of one or more RBC transfusion compared to late EPO but significantly increased risk of ROP.[79]

In conclusion, rHuEPO is effective in stimulating erythropoiesis in preterm infants, as evidenced by increased reticulocytes and haematocrit. Very low birth weight infants have the greatest RBC transfusion requirements as well as large phlebotomy losses in the first 2-3 weeks of life. rHuEPO will take 1-2 weeks before any benefit in packed cell volume is seen.[4,59]-

Section 6 Special considerations in the selection and provision of RBC units for neonatal transfusion

6.1 Age of RBC units

Previously, the tradition was to use relatively fresh RBCs to transfuse preterm infants which resulted in exposure to multiple donors. This was the practice because of concerns about hyperkalaemia in stored blood, the decline in pH and RBC 2,3-DPG levels, and a theoretical possibility of shortened survival in vivo of older stored RBCs. The extracellular potassium content of blood rises steeply with storage reaching concentrations of 60 mmol/l by day 35 in SAG-M stored RBCs. Theoretical calculations predict that the amount of transfused potassium would not be of clinical significance in the small volume setting provided blood was transfused slowly. There are now numerous studies demonstrating the safety of assigning to an infant at the time of first transfusion a unit of blood which was divided into aliquots or from which aliquots could be drawn as required and used up to its full shelf life 35-42 days of age.[83-90] Such systems have led to a dramatic decrease in donor exposure.

The potassium content of stored blood is of concern in the large volume transfusion setting i.e. > 25ml/kg of RBCs, or greater than one blood volume in 24 hours such as occurs in exchange transfusion. Rapid transfusion of RBCs with high extracellular K^+ can result in fatal cardiac disturbances in small infants, particularly if infused through a central line. Fatal hyperkalaemia has occurred following the rapid infusion of 32-day old RBCs.[91]

It is prudent to use blood with low levels of potassium (< 5 days old) in infants who require large volume transfusions or who have documented hyperkalaemia or renal failure. Irradiated red cells induce a more rapid leakage of potassium during storage than unirradiated red cells. A case of hyperkalaemia-induced cardiac arrest occurred in a 62 day old baby girl following the rapid infusion through a central line of 120 mls of 6 day old red cells which had been irradiated 48 hours previously.[92] (see section 9.3 on the effect of irradiation on red blood cells)

The 2,3DPG content of stored blood is completely depleted by 21 days causing the p50 to decrease from 27 mm Hg in fresh blood to 18 mm at the end of storage which is the same as the p50 of premature infant's red blood cells which contain high levels of Hb F. Transfused RBCs rapidly regenerate 2,3 DPG within hours of transfusion.

6.2 RBC anticoagulant/preservative solutions

6.2.1 SAG-M RBCs for small volume top-up transfusion of neonates

For many years in the past citrate, phosphate, dextrose (CPD) was used to store RBCs for all neonatal transfusions. Luban et al in 1991 estimated that additive solutions such as SAG-M (saline, adenine, glucose, mannitol) in which RBCs are stored, should, on theoretical calculations, present no substantive risk to the pre-term infant in the small volume RBC transfusion setting [93] and their safety has been demonstrated subsequently in a number of studies.[86-89] Most red cell transfusions in neonates are small volume top-up transfusions using packed cells in SAG-M in so-called 'Pedipack' splits.

6.2.2 SAG-M RBCs for large volume surgery related transfusion of neonates

Luban et al also estimated that concentrations of the solutes in blood such as SAG-M might well reach dangerous or toxic levels in the setting of massive transfusion.[93] There were theoretical concerns about the concentrations of adenine and mannitol, which can cause nephrotoxicity in laboratory animals when used in high concentrations, as well as the diuretic effects of mannitol and its possible effects on intracerebral pressure.[93, 94] Several of the major paediatric cardiology centres in the UK and the one centre in Dublin have used SAG-M red cells for neonatal cardiac surgery for many years; other UK centres use CPD blood with no reported differences in outcome. A recent prospective, randomized, controlled trial of fresh whole blood compared with reconstituted blood (red cells in additive solution combined with FFP) for 200 infants (< 1 year) has been published.[95] The use of fresh whole blood for cardiopulmonary bypass priming had no advantage over the use of a combination of packed cells and FFP during surgery for congenital heart disease. Moreover, circuit priming with fresh whole blood was associated with an increased length of stay in the intensive care unit and increased perioperative fluid overload. There was no significant difference in the number requiring renal replacement therapy. Neonates (< 28 days old) constituted 39% of the study group, and a post-hoc subgroup analysis by patient age comparing those < 28 days vs > 28 days old again found no difference in outcome.[95]
Because of current concerns over transfusion transmission of vCJD, it is important to consider the implications of the greater plasma volume in CPDA-1 blood as compared to SAG-M blood.[96] This may result in an increase in the estimated risk of vCJD transmission. The national neonatal cardiac surgery centre in Our Lady's Hospital, Dublin, has for many years been using red cells in SAG-M, stored for less than 6 days, for infants undergoing cardiac surgery with no reported problems. Continued use of this product is recommended for neonatal cardiac surgery. The IBTS will provide such a RBC component for other large volume transfusions in infants undergoing surgery with a neonatal specification and a 5 day shelf-life for this indication.

6.2.3 Exchange transfusion, massive transfusion in acute life-threatening blood loss, and ECMO: CPDA-1 versus SAG-M RBCs

SAG-M blood, unlike CPDA-1 blood contains virtually no coagulation factors or albumin. As outlined in the Blood Users Group Massive Transfusion Guidelines, coagulopathies are common in the massive transfusion setting particularly with SAG-M RBCs.[97] Because infants have a physiological deficiency of clotting factors, greater problems with coagulopathies could be anticipated than in the older child or adult. Currently, the continued use of CPDA-1 RBCs, less than 5 days old, is recommended for the massive transfusion of neonates during exchange transfusions. Although there is a lack of evidence on which to guide practice, the IBTS will also make available CPDA-1 RBCs for massive transfusion in life-threatening haemorrhage in newborn infants. If CPDA-1 RBCs are not available, (see Section 4.4 acute blood loss) red cells in additive solution (SAG-M), ≤ 5 days old, are suitable. Clinicians should be aware that SAG-M blood contains virtually no coagulation factors and FFP (or SD-Plasma) may be required *(level IV evidence, grade C recommendation).*

Extracorporeal membrane oxygenation (ECMO) is a complex, risky, extracorporeal life support system which artificially provides oxygenation and /or perfusion through a mechanical pump to which the patient is attached. Indications for ECMO are beyond the scope of this guideline. The provision of ECMO services in this country is currently limited to the post-bypass care of infants undergoing cardiothoracic surgery with cardiopulmonary bypass; infants from this country who require ECMO for other indications are transported abroad. Infants undergoing ECMO are prone to bleeding, particularly intracranial haemorrhage, the causes of which are multifactorial but include systemic heparinisation, activation and consumption of platelets due to exposure of blood to artificial surfaces and patients often require platelet and FFP support in addition to red cell requirements. Because standard transfusion practices are lacking, individual ECMO centres establish their own specific criteria for transfusion and blood component selection. Some centres use RBCs which also contain plasma such as CPD, others SAG-M with FFP, but it seems reasonable that RBCs should be not more than 5 days old in order to minimize the risk of hyperkalaemia.[51]

6.3 Dedicated units for serial neonatal transfusions

It is recommended that a preterm infant judged to require a small volume transfusion should be assigned to a relatively fresh (less than 5 to 7 days old) RBC unit at the time of first small volume transfusion. Aliquots from that same unit, prepared by a technique to ensure sterility or pre-made Pedipacks, should be used for subsequent small volume, slowly administered transfusions up to the expiration date (35 days) of the unit of RBCs. Protocols are designed so that the freshest blood is transfused to the youngest pre-term infants i.e. the VLBW infant ages with the unit.[98]

The Pedipack system is designed to reduce donor exposure in the multitransfused infant. In the Irish Blood Utilisation Survey of 2001, details were supplied for 386 infants transfused with Pedipacks. The transfusion requirements for 64% of all infants were met from one donor with a mean overall donor exposure of 1.6.[99] The ideal goal is one donor exposure per infant. Lowering donor exposure to less than 1.1 may not be possible in transfused very low birth weight infants.[4,89] A theoretical concern exists that if a reserved RBC unit was contaminated, the infant may receive several doses of that pathogen,[94] however the previous practice of sharing a fresh unit among infants resulted in multiple transmissions from an infected donation.[100]

6.4 Pre-transfusion testing for neonates and infants withinthe first four months of life.

Although the mechanism is unclear, RBC alloantibody formation in infants of less than 4 months of age is extremely rare. Two serological reports involving 143 multitransfused infants followed for up to 30 months failed to detect alloantibody formation.[101,102]

Repeat samples for red cell compatibility testing for infants younger than 4 months are not required, provided that initial antibody screening methods reveal no antibodies and only small volume transfusions have been administered. However, red cell alloantibody anti-E has been detected in an 11-week-old infant following a massive transfusion[103]and repeat compatibility testing following large volume transfusions is recommended.

6.4.1 Pre-transfusion Compatability testing[51]

* Wherever possible, samples from both mother and infant should be obtained for initial ABO and RhD group determination.

Investigations on the maternal sample:

- ABO and RhD group
- Screen for the presence of atypical red cell antibodies*

Investigations on the infant sample:

- ABO and RhD. ABO by cell group only, repeated on same sample if no historical result (a reverse group would detect passive maternal antibodies due to relative deficiency of isohemagglutinin production in the neonate).
- Direct antiglobulin test (DAT) performed on the neonate's red cells*
- In the absence of maternal serum, screen infant's serum for atypical antibodies by an indirect antiglobulin technique (IAT).

*A positive DAT on the neonate's red cells or an atypical red cell antibody in maternal or neonatal serum suggests possible haemolytic disease of the newborn (HDN). In such cases, serological investigation and full compatibility testing will be necessary to allow selection of appropriate blood. *(level IV evidence, grade C recommendation).*[51] However babies of unsensitised RhD negative mothers who have received ante-natal prophylaxis with anti-D may be born with a positive DAT. The BCSH now recommends that where the mother has received ante-natal anti-D, the DAT on the cord blood should only be performed if the mother has additional red cell allo-antibodies or as an investigation into haemolytic disease of the newborn, for example if the baby is jaundiced or anaemic.[96]

Section 7 Component specification for RBC transfusion

Donors

Blood components intended for transfusion to the fetus or infant under four months must be prepared from blood donated by donors who have given at least one previous donation within the past 2 years, which was negative for all mandatory microbiological markers.

7.1 Component specifications for red blood cells for small volume transfusion:[51]

- ABO compatible with mother and infant, and infant's RhD group (or RhD neg)
- IAT compatible with maternal plasma (if available) or neonate's plasma for first transfusion (& subsequent transfusions if atypical maternal antibodies are present).
- SAG-M - use up to full 35 day shelf-life *(level Ia evidence, grade A recommendation)*
- Haematocrit (Hct) 0.50-0.70
- Infuse in a volume 10-20 mls/kg over 2 to 4 hours *(see section 5.2)*
- Aliquotted donation (Pedipack) from a single unit dedicated to one infant *(level Ib evidence, grade A recommendation)*

- Irradiated if appropriate (see section 9)
- CMV seronegative
- Small volume transfusions can be given repeatedly over the first 4 months of life without further serological testing, provided that there are no atypical maternal red cell antibodies in the maternal/infant serum, and the infant's DAT is negative when first tested.
- Transfusion should be through a standard blood giving set with a clot screen filter (170-200 μ) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used.[51]

7.2 Intrauterine fetal transfusion (IUT)

Intrauterine red cell transfusions are performed primarily to treat fetal anaemia caused by red cell alloimmunisation (most important antigen RhD, followed by c and K) or less commonly, for fetal anaemia secondary to parvovirus infection.[51] Intrauterine platelet transfusions may be indicated to treat fetal thrombocytopenia caused by platelet alloimmunisation (see section 8.5.1: Neonatal Alloimmune Thrombocytopenia). We recommend that intrauterine fetal transfusions of RBCs or platelets should only be performed in a specialised tertiary centre[51] *(grade A recommendation).*

Transfusion in utero appears to reduce significantly the requirement for transfusion postnatally.[104,105] Babies who are born at an adequate gestation for lung maturity, with an adequate Hb and with the majority of fetal blood having been replaced by donor cells, (% of fetal cells about 1%) normally require little specific management. Jaundice is usually mild and phototherapy alone may suffice. Many require simple top-up transfusions for hyporegenerative anaemia, which may be, prolonged.[104] Babies who are born without complete suppression of fetal haemopoiesis will be at greater risk of both neonatal anaemia and hyperbilirubinaemia. This group may still have significant haemolytic anaemia at birth requiring phototherapy and exchange transfusion.

It is important to be aware that post natal transfusions in infants who have undergone transfusion in utero must be irradiated to prevent transfusion acquired graft versus host disease (TA-GVHD) (see section 9.4 indications for the gamma-irradiation of cellular blood components).

7.2.1 Red cell component specifications for IUT:

- Group O (low titre haemolysin), RhD negative and Kell negative to reduce additional maternal alloimmunization risks. In exceptional cases, e.g. for haemolysis caused by maternal anti-c, RhD positive (R1,R1), c-negative blood will be necessary.[51]
- IAT-cross-match compatible with maternal serum and negative for the relevant antigen(s) determined by maternal antibody status.[51]
- Less than 5 days old and in citrate phosphate dextrose (CPDA-1) anticoagulant
- CMV seronegative
- Irradiated (must be transfused within 24 hours of irradiation)
- Haematocrit should be between 0.70 and 0.85 [18,96]
- Should not be transfused straight from 4^0C storage. Use of a thermostatically controlled device manufactured and approved for blood warming is recommended.
- Transfusion should be through a standard blood giving set with a clot screen filter (170-200 μ) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used.[51]

7.3 Exchange transfusion

Exchange transfusion in the neonatal period is carried out to prevent bilirubin encephalopathy (kernicterus) secondary to severe hyperbilirubinemia and/or to manage severe anaemia at birth, particularly in the presence of heart failure. Isoimmune haemolytic disease of the newborn (HDN) is the commonest cause of severe hyperbilirubinemia and may cause severe anaemia and hydrops fetalis.

Anti-D immunoglobulin prophylaxis has been extremely effective in preventing HDN secondary to pregnancy related RhD sensitisation. In addition, the antenatal management of RhD sensitised pregnancies and more aggressive management of jaundice in the newborn with intensive phototherapy has dramatically decreased the need for neonatal exchange transfusion.

There has been an increase in severe hyperbilirubinemia and encephalopathy in infants who are discharged home shortly after birth and who become severely dehydrated and jaundiced as a result of inadequate intake of breastmilk. Recommended serum bilirubin levels for exchange transfusion have been recently published by the American Academy of Pediatrics and vary depending on the clinical context.[106] In almost all cases, exchange transfusion is recommended only after intensive phototherapy has failed to control serum bilirubin levels.[106] High dose intravenous immunoglobulin has been shown to reduce the need for exchange transfusions in Rh and ABO haemolytic disease[107-110] and may offer a newer adjunct/alternative to exchange transfusion in haemolytic disease of the newborn.[106]

7.3.1 Risks of exchange transfusion.

Exchange transfusion in the neonate constitutes a massive transfusion involving the replacement of one or two whole blood volumes. Complications occur related to the transfusion itself including hypocalcaemia, hyperkalaemia, and bleeding from thrombocytopenia as well as inherent complications of an umbilical catheter including air embolus, portal vein thrombosis and sepsis. Metabolism of citrate produces bicarbonate that may result in alkalosis and subsequent hypokalaemia. Death associated with exchange transfusion has been reported in approximately 3 in 1000 procedures.[111,112] Significant morbidity (apnoea, bradycardia, cyanosis, vasospasm, hypoglycaemia, thrombosis, necrotising enterocolits) occurs in as many as 5% of exchange transfusions.[111] Exchange transfusion was associated with a mortality of 2% in 106 patients evaluated over a 15-year interval by Jackson et al; serious complications developed in 12% of patients; more than 34% of infants had documented hypocalcaemia during exchange, one in 20 infants demonstrated electrocardiographic changes, and one had a cardiac arrest.[113] Hypothermia and immature liver function impair citrate metabolism. Because exchange transfusion is now rarely performed, risks in the current era are hard to quantify.[106] Exchange transfusion should be performed only by trained personnel in a Neonatal Intensive Care Unit with full monitoring and resuscitation capabilities[106] and may be an indication for tertiary referral. *(grade A recommendation)*

7.3.2 Red cell component specifications for exchange transfusion:

- Group O or ABO compatible with maternal and neonatal plasma, RhD negative. In cases of HDN due to maternal anti-c, RhD positive (R1R1) c-negative blood should be used.
- Negative for any red cell antigens to which the mother has antibodies[51]
- IAT-cross-match compatible with maternal plasma
- 5 day old or less (to ensure optimal red cell function and low

supernatant potassium levels)
- Collected into CPDA-1 anticoagulant
- CMV seronegative
- Irradiated and transfused within 24 hours of irradiation. Irradiation is essential if the infant has had previous IUT and is recommended for all exchange transfusions. Irradiation for exchange transfusion in the absence of IUT is not essential if this would lead to clinically significant delay.[51]
- Haematocrit of 0.50-0.55; packs to be labelled with actual Hct of the unit

There is no consensus among neonatologists on the appropriate haematocrit (Hct) for ET. Whole blood, with a Hct of 0.35-0.45 may result in a post exchange HB < 12g/dl in a severely anaemic baby and thus increase the risk of a subsequent top-up transfusion and increased donor exposure, but as the neonate will have adult haemoglobin post exchange, there will be increased oxygen delivery compared to HbF. The US guidelines recommend whole blood or reconstituted whole blood.[1] The advantages of whole blood for exchange is a lower risk of making the baby polycythaemic and one donation may suffice for a double-volume exchange for hyperbilibubinaemia. A component with a Hct of 0.5-0.55 as recommended in the updated BCSH guideline should suffice for neonatal exchange for both hyprbilibubinaemia and anaemia *(level IV evidence, grade C recommendation)*.[96] To avoid the production of units where the Hct is too high, the packs will be individually labelled with their Hct.

- Blood should not be transfused straight from 4^0C storage. Since exchange transfusion is considered a massive transfusion, this is a situation in which a thermostatically controlled device manufactured and approved for blood warming should be used.
- Transfusion should be through a standard blood giving set with a clot screen filter (170-200 μ) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used.[51]

7.4 ABO haemolytic disease of the newborn

ABO maternal-fetal incompatibility involving group O mothers, whose sera contain IgG anti-A and anti-B, is estimated to be present in about 15% of Group O pregnancies. ABO HDN occurs only in about 3% of all births. Typically ABO HDN causes mild postpartum jaundice, which is detected 24 hours after delivery and can be managed without transfusion; haemolysis severe enough to cause hydrops is very rare. Unlike Rh disease, ABO HDN can affect the first-born. Only 10% of DAT-positive, ABO-incompatible maternal-fetal pairs developed clinically significant ABO HDN but 80% of infants with clinically significant haemolysis had a positive DAT with a positive eluate obtained in all but one of the remaining affected infants.[114] The DAT may be negative in mild to moderate ABO HDN and should be repeated if negative in the first sample. Often, however, the diagnosis is one of exclusion: a relatively low cord blood Hb which continues to fall, a raised bilirubin level, group O mother and the infant group A (occasionally group B especially in mothers of black African origin where IgG anti-B antibodies have given rise to severe fetal anaemia[115]), positive DAT in the absence of any other alloantibodies.[51] Spherocytes are prominent on a blood smear. A high titre IgG anti-A or anti-B in the mother is supportive evidence but a low titre does not exclude the diagnosis.

Group O blood, with low titre plasma anti-A and anti-B, compatible with maternal plasma should be used for transfusion. If an exchange transfusion is required in ABO HDN, this should be with group O cells with low titre plasma anti-A and anti-B.[51] *(level IV evidence, grade C recommendation).* Group O red cells resuspended in AB plasma can be used but this results in exposure to two donors.

Section 8 Neonatal Thrombocytopenia

8.1 Aetiology

The circulating platelet count in healthy neonates is similar to that found in older children and adults, the normal range is between 150 to 400 x 10^9/L and platelet counts of less than 150 x 10^9/L should be considered abnormal. Although capillary platelet counts (obtained, for example, by heel puncture) correlate well with platelet counts in simultaneously collected venous blood samples, a result may be erroneously-low because of platelet aggregation in the puncture site. Confirmation of thrombocytopenia requires an anticoagulated venous sample and inspection of a blood film to exclude platelet clumping.

Apart from anaemia due to iatrogenic blood loss, thrombocytopenia is the commonest haematological abnormality in the neonatal period with over 75% of episodes occurring in the first 72 hours of life.[116] A complete review of the aetiology and investigation of the many causes of neonatal thrombocytopenia is outside the scope of this review and readers are referred to an excellent review of Roberts (2005).[117] The highest incidence occurs in sick low-birth-weight preterm babies. The responsible mechanisms are unclear in a substantial proportion of the latter and are probably multifactorial.

Most episodes of thrombocytopenia in preterm infants are discovered following routine blood counts during intensive care. This early thrombocytopenia has a consistent pattern with a platelet nadir around day 4 and a recovery of platelet numbers by day 7-10 of life.[118] Severe thrombocytopenia, platelet nadir < 50 x 10^9/l, is unusual and platelet recovery is spontaneous.[118] An important mechanism for this early thrombocytopenia is thought to be impaired platelet production as evidenced by decreased numbers of clonogenic megakaryocyte progenitors and relatively low levels of thrombopoietin (Tpo) suggesting an impaired Tpo response to thrombocytopenia.[119-122] Affected thrombocytopenic preterm infants are typically born following pregnancies complicated by placental insufficiency and/or fetal hypoxia.[118]

An important cause of early severe thrombocytopenia (platelets < 50 x 10^9/L) at birth in a term or preterm infant is neonatal alloimmune thrombocytopenia (NAIT, see section 8.5.1). Sepsis is the commonest clinical condition precipitating late onset thrombocytopenia (> 72 h of age) in preterm infants. Sepsis-associated thrombocytopenia is often severe, platelet count < 50 x 10^9/l, rapidly progressive, prolonged and may occur with or without DIC.[118, 123]

Two studies have shown a ten fold or higher mortality in infants who require one or more platelet transfusions, compared to nontransfused infants.[124,125] Del Vecchio, showed that 9.4% of a total of 1389 patients admitted to the NICU received one or more platelet transfusions; 48% received 1 platelet transfusion, while 52% received more than one.[124] In none of the neonates who died was haemorrhage the direct cause of death suggesting that severe thrombocytopenia in neonates should be considered a marker of overall disease severity.

Intracranial haemorrhage in the form of periventicular-intraventricular haemorrhage (PIVH) occurs in sick preterm infants most commonly in the first 24 hours, with almost all developing by 72 hours of life. The aetiological role of thrombocytopenia as a risk factor and the therapeutic benefit of platelet transfusions has not been established.[7] The one randomised controlled trial of platelet transfusion in neonates which assigned thrombocytopenic premature infants to a group who were transfused whenever

the platelet count fell below 150,000 x 10^9/l, versus transfusing platelets only when platelet count fell to <50 x 10^9/l, showed no difference in the frequency of intracranial haemorrhage between the two groups(28% vs.26%).[126]

8.2 Guidelines for neonatal platelet transfusions

The relative risks of different degrees of thrombocytopenia in various clinical settings in infancy are largely unknown. Establishing a threshold for prophylactic platelet transfusion in the neonate is particularly difficult because of the large number of variables in addition to the platelet count.[127] These include:

The gestational age - preterm infants have a higher risk of bleeding and lower levels of clotting factors;

The degree of illness e.g. sepsis, necrotising enterocolits (NEC), liver, renal function;

The presence of other coagulation abnormalities e.g. DIC;

Use of medications which impairs platelet function e.g. indomethacin which is frequently administered to close a patent ductus arteriosus or to prevent IVH.

Table 5. Suggested platelet transfusion thresholds for infants under 4 months of age
(level 1V evidence, grade C recommendation)

20-30 x 10^9/l	For prophylaxis, clinically stable preterm or term infant, not bleeding (BCSH, 2004)*
30 x 10^9/l	Sick preterm or term infant not bleeding (BCSH, 2004)[51]
30 x 10^9/l	Minimum platelet count in infant with NAIT because the HPA antibody can impair platelet function (see Section 8.5.1)[51]
50 x 10^9/l	First week of life in very small preterm infant [117]
50 x 10^9/l	Preterm or term neonate, with bleeding (BCSH, 2004)[51]
50 x 10^9/l	Invasive procedure
50-100 x 10^9/l	Clinically unstable, DIC, major surgery, massive blood loss /massive transfusion
< 100 x 10^9/l	Infant undergoing ECMO; higher platelet threshold if bleeding [51,1]

*`There is little evidence base to guide practice in this area. The US guidelines quote a 30 x 10^9/l trigger.[1] The BCSH recommends a 20 x 10^9/l in this setting with a qualification that a higher threshold (level not cited) is required in small, preterm babies, particularly during the first few days of life or if there is a co-existent coagulopthy.[51]

8.3 Platelets for neonatal transfusion (ABO and Rh Groups)

Infant and donor should be ABO identical or compatible. Where ABO identical platelets are not available, group A platelets are preferable for Group B recipients and vice versa. Platelets should not have high titre haemolysins.*
Group O platelets are the least suitable group for non-Group O infants as passive anti-A or anti-B may lead to haemolysis in infants who have small blood volumes. The UK Serious Hazards of Blood Transfusion (SHOT) has reported two cases of haemolysis after platelet concentrates of Group O were transfused to non-group O children.[128] Also, the International Forum on transfusion of apheresis platelets and ABO blood groups, concludes that the transfusion of group O platelets to non-O recipients should be avoided unless other requirements such as human leucocyte antigen (HLA) or human platelet antigen (HPA) compatibility, make only group O platelets available.[129] If Group O Platelets are the only available product, they should be negative for high titre anti-A/anti-B.* In addition the supernatant plasma should be reduced and the volume replaced with saline or platelet additive solution to reduce the risk of haemolysis. This component should be used as soon as possible. The number of incompatible platelet transfusions should be limited to one dose where possible.
* An absence of high titre haemolysins does not guarantee absence of haemolysis risk. There is no standard method for determining what constitutes 'high titre' of ABO antibody in blood donations.[96,130] Components from group O donors with 'low titres' of anti-A, anti-B, and/or anti-A,B, can cause intravascular haemolysis in non-group O recipients if given in sufficiently large volumes.[130] Some normal individuals, mostly of group O, have plasma with ABO antibodies which although highly active clinically are in relatively low titres and may escape detection by dilution tests in vitro.[96] Therefore, recipients, who are not Group O, will remain vulnerable to ABO- related haemolysis following the administration of group O platelet concentrates suspended in plasma from such donors.[96]
RhD negative platelets should be given where possible to RhD negative patients but especially female infants.

Anti-D immunoglobulin should be administered to any RhD negative female of childbearing potential in receipt of RhD positive platelets. A dose of 150 IU of intravenous anti-D covers for up to ten 50 ml infusions of RhD positive platelets over a period of 6 weeks (based on 50 IU/250 mls adult pack). Nevertheless, if a unit of RhD positive platelets has to be given and followed by anti-D prophylaxis, and if further treatment with platelet concentrates is required, RhD negative platelets are preferred and recommended.[96]

Platelets are usually infused in infants in a volume of 10-20 ml/kg. Platelets should be transfused through a standard blood giving set with a screen filter (170-200) or an alternate system incorporating the same filtration. Where small volumes are drawn in to a syringe an appropriate filter must be used.[51]

8.4 Platelet component specifications:

- Platelets for neonatal use supplied by the IBTS are apheresis-derived from a single donor. At present, the neonatal apheresis platelet pack is split into two aliquots using a closed system to reduce donor exposure. The current shelf-life of platelet concentrates is 5 days. With the implementation of bacterial testing of platelets and the extension of the shelf-life of apheresis platelets to 7 days, it will be possible to subdivide a donation into 4 aliquots to reduce further donor exposure in infants who require repeated platelet transfusion.
- Components should be free of clinically significant irregular blood group antibodies, including high titre anti-A and anti-B, (but see section 8.3 above).
- CMV seonegative. However, in an emergency, or where Human Platelet Antigen (HPA) or Human Leucocyte Antigen (HLA) matched platelets are required, and CMV-seronegative blood components are not available, the transfusion of leucoreduced components that have been tested to ensure a residual leucocyte count of < 1x10^6 is acceptable *(level IIb evidence, grade B recommendation).* (see also section 2.1.3)
- All platelets for neonatal use are irradiated by the IBTS to prevent the rare risk of TA-GVHD. Unlike the situation with RBCs, irradiation has no effect on the platelets (see Section 9 on Irradiation).

8.5 Neonatal immune thrombocytopenia

8.5.1 Fetal/Neonatal Allo-immune Thrombocytopenia (FNAIT)

Background

The most important cause of severe thrombocytopenia (platelets < 50 x 10^9/L) at birth in an otherwise well baby is neonatal alloimmune thrombocytopenia. This arises following maternal sensitisation to paternal antigens present on fetal platelets.[131] The maternal alloantibody produced does not react with the mother's platelets but crosses the placenta and destroys fetal platelets. The paternal derived fetal platelet antigen target, against which the maternal alloantibody is directed, is usually HPA-1a, which is present on platelets of 98% of the population and is responsible for FNAIT in approximately 80% of cases.[132] The second most common platelet antigen involved in FNAIT is HPA-5b.[133] Less commonly implicated antigens accounting for the remaining 5% in the Caucasian population include HPA 3a and HPA 15a and 15b. Antigen frequencies vary in different ethnic groups and so the ethnic origin of suspected cases should be considered when investigations are performed. Very rarely the cause is due to antibodies to low incidence or private platelet antigens.

Results from screening studies show that severe FNAIT due to anti-HPA-1a occurs in approximately 1 in 1,200 births in the UK and 1 in 1100 in Ireland.[134,135] However the clinical detection rate is much lower with only 1 case in 16,500 births observed in a study of Irish hospitals suggesting under- recognition of the disorder.[136] Certain HLA types are associated with alloantibody formation, for example, women who have the HLA-DR3*0101 antigen account for the majority of affected cases of HPA-1a induced FNAIT.[134,137] A similar finding is seen with the HPA 5b antigen and HLA-DRw6.[138]

8.5.2 Clinical presentation

Whilst FNAIT is in other ways analogous to haemolytic disease of the newborn due to RhD or ABO incompatibility, in FNAIT, the first child is usually affected with thrombocytopenia.[131] FNAIT typically presents as an isolated severe thrombocytopenia in an otherwise healthy child at birth. The neonate usually presents with petechiae or is found to have a low platelet count by chance. Visceral haemorrhages are less common. Intracranial haemorrhage (ICH) is the most serious complication, the reported incidence of which varies from 7% to 20%, of which 50% occur in utero.[132,139] More unusual presentations include unexplained hydrocephalus, ventriculomegaly, porencephalic cysts, optic hypoplasia, hydrops fetalis and intrauterine death in second and third trimesters.[140]

8.5.3 Diagnosis

Diagnosis of FNAIT is usually made on clinical grounds, depending on the exclusion of other causes of neonatal thrombocytopenia such as bacterial and fungal sepsis, NEC, intrauterine growth retardation, congenital infections (CMV, toxoplasma, rubella), maternal autoimmune (ITP, SLE), severe HDN or chromosomal anomalies.[117] A study of 222 cases of neonatal thrombocytopenia identified three criteria which distinguishes cases of FNAIT from other causes of thrombocytopenia. These were: (1) severe thrombocytopenia, platelet count < 50 x 10^9/l; (2) ICH associated with one or more of: a 1-min Apgar score > 5, birthweight > 2.2 kg, grade >1, antenatal occurrence, or signs of bleeding i.e. petechiae, ecchymoses; and (3) absence of additional medical problems.[141] Making the distinction from autoimmune causes is usually facilitated by the maternal platelet count, in that the mother has thrombocytopenia not thought to be gestational (platelet count <100 x 10^9/l) or there is a history of immune thrombocytopenic purpura. The laboratory diagnosis of FNAIT involves platelet antigen typing of the parents, which shows that the antigen present on the father's platelets is absent on the mother's platelets and the mother's serum demonstrates antibody activity to the antigen using indirect immunofluorescence assay,[142]or enzyme-linked immunoassay or monoclonal antibody–specific immobilization (MAIPA).[143] The antibody assay must have the ability to detect anti-HPA-15 antibodies and where there is a strong clinical suspicion of FNAITP, screening for antibodies to low incidence and private antigens using the paternal platelets as the antigen source should be performed. It should be remembered that failure to detect a platelet-specific alloantibody in the maternal serum does not exclude the diagnosis.

8.5.4 Postnatal management of FNAIT *(evidence level III, grade C recommendation)*

Treatment should not be delayed pending the results of investigations as some may take days to complete and the risk of cerebral bleeds is highest in the first 48 hours after delivery. The trigger for platelet transfusion is higher than for other causes of neonatal thrombocytopenia (platelet count of 30 x 10^9/l) due to associated platelet dysfunction.[51] The treatment of choice is the transfusion of HPA compatible platelets. Data from 600 cases analysed at the Oxford and Cambridge platelet immunology laboratories suggest HPA 1a, 5b negative platelets are compatible in 95 % of cases.[144] However, the provision of HPA compatible platelets is a logistical challenge for the IBTS along with other transfusion services because of the low frequency (approx 2.5%) of HPA-1a negative donors.

Cerebral ultrasound should be performed in all cases of severe thrombocytopenia (platelet count < 30 x 10^9/l) to exclude the presence of an intracranial haemorrhage. The platelet count should be repeated post transfusion to confirm that an increment has been obtained and daily thereafter until a stable or rising count has been achieved. The duration of thrombocytopenia is usually between 1 and 2 weeks but prolonged thrombocytopenia up until 6 weeks may occur.

If suitable matched platelets are not immediately available or the antibody cannot be identified, consideration should be given to transfusing random donor platelets. The use of random donor platelets was regarded as a suboptimal approach to treatment (BCSH UK platelet transfusion guidelines, 2003).[145] However, a recent retrospective study on the use of antigen positive, random donor platelets in FNAIT unexpectedly showed that 24 out of 27 newborns had a platelet increment above 40 x 10^9/l, with moderate platelet increments in 8 or significant (> 80 x 10^9/l) in 16 infants.[146] The authors conclude that the transfusion of platelet concentrates from random donors is an appropriate strategy in the management of unexpected, severe NAIT cases, pending the availability of compatible platelets.

A further strategy for the situation where compatible platelets are not readily available or the antibody cannot be identified, is to collect maternal platelets which must be irradiated and washed (to remove antibody-laden plasma) before use.[144,147,148] There are logistical problems with the provision of maternal platelets; lack of apheresis facilities on site and delays associated with donation.

The role of high dose (1g/kg) intravenous immunoglobulin therapy (IVIG) given on two consecutive days is also limited in that a response takes up to two days to take effect and may only occur in 75% of cases.[149-151] IVIG may be considered in cases of severe prolonged thrombocytopenia where problems in the supply of HPA compatible platelets are anticipated. In those cases of known FNAIT, where elective delivery is performed, HPA compatible platelets should be ordered in advance from the blood transfusion service.

8.5.5 Follow-up

The diagnosis and implications for future pregnancies should be explained to the parents. The recurrence rate is based on the paternal zygosity for the implicated antigen. A 100% recurrence is expected if the father is homozygous or 50% if heterozygous. The disease is likely to be as severe if not more severe than the index case. Referral to a Fetal Medicine Specialist with expertise in alloimmune disorders including FNAIT should be arranged early in subsequent pregnancies. Fetal alloantigen genotyping can be carried out on chorionic villous amniotic fluid or fetal blood samples to determine the fetal type where the father is heterozygous. Either maternal therapy with intravenous immunoglobulin +/- steroids or fetal platelet transfusions may be administered based on the severity of the disorder in the previous sibling and response to treatment. A detailed analysis of the antenatal management of FNAITP is beyond the scope of this document and the reader is referred to recent papers on the subject.[152-156]

8.5.6 Recommendations for postnatal management of FNAIT in neonate *(Evidence level III, grade C recommendation)*

- Treatment should not be delayed pending the results of investigations
- The treatment of choice is the transfusion of HPA compatible platelets
- HPA 1a and 5b negative platelets which are compatible in 95 % of cases should be provided for transfusion in all cases of suspected FNAIT
- Transfusion of random donor platelets is an appropriate strategy in the management of severe, unexpected FNAIT, pending the availability of compatible platelets.[146,96]
- Failure to detect a platelet-specific alloantibody in the maternal serum does not exclude the diagnosis. Where FNAIT is strongly suspected the investigations should include screening of the maternal serum against paternal platelets to test for antibodies to low incidence antigens. In addition, a repeat antibody screen of the maternal serum should be performed four weeks later to identify weak antibodies which may not have been detectable at delivery.
- Early referral to a Fetal Medicine Specialist with expertise in FNAIT should be made in subsequent pregnancies

8.5.7 Maternal autoimmune thrombocytopenia (AIT)

Autoimmune thrombocytopenia is due to the passive transfer of autoantibodies from mothers with isolated immune thrombocytopenic purpura (ITP) or it may be seen in association with other autoimmune conditions such as maternal systemic lupus erythematosus. Unlike FNAIT, the specificity of the platelet antibody seen in AIT is towards antigen(s) common to maternal and fetal platelets. Approximately 1 in 10,000 pregnancies are complicated by maternal ITP.[157] The risk of significant infant morbidity and mortality is minimal, as the infant platelet count is rarely less than 50 x 10^9/1, ICH rarely if ever happens and when it does occur it is not related to birth trauma.[157,158] It is also clear that there is no correlation between the platelet count and level of autoantibody seen in the mother to the severity of thrombocytopenia observed in the infant. In fact it has been well documented that women with normal platelet counts following splenectomy for ITP still deliver babies who are thrombocytopenic.[159]

The bleeding manifestations including the risk of ICH in children of mothers with AIT are significantly less than in children with FNAIT. These infants are usually very well and born at term. The neonatal platelet count often falls after birth to a nadir on days 1–3 and it is during this time frame that bleeding occurs.[160] Spontaneous recovery of the infant platelet count is usually observed within 3 weeks after birth. However, if the platelet count is below 20 x 10^9/1 or if there is significant bleeding then intravenous immunoglobulin (1g/kg/) should be given on two consecutive days and if this fails to raise the platelet count then a short course of prednisolone (2-4mg/kg/day PO) for 7-14 days should be added.[161] Platelet transfusions should be reserved for the treatment of life- threatening haemorrhage (ICH) and larger doses are required due to the poor survival of donor platelets in the baby's circulation.[145] Further aspects of the antenatal management of maternal AITP are covered in the guidelines for the management of ITP (BCSH).[162]

Recommendation

In neonatal thrombocytopenia due to maternal AITP platelet transfusions should be reserved for the treatment of life-threatening haemorrhage (ICH). Larger doses are required due to the poor survival of donor platelets in the baby's circulation and should be given in conjunction with intravenous IgG.

Section 9 Transfusion Acquired Graft Versus Host Disease (TA-GVHD)

Transfusion-associated graft versus host disease (TA-GVHD) is a rare but usually fatal immunological transfusion complication occurring 1-6 weeks after transfusion. TA-GVHD results from the engraftment of donor T lymphocytes in a recipient who is unable to reject them. The disease, which is an immunological response against the host, targets the skin, liver, gastro-intestinal tract and bone marrow manifesting as fever, erythematous skin rash, diarrhoea, abnormalities of liver function and pancytopenia secondary to bone marrow aplasia. Immunocompromised transfusion recipients are at risk. Among immunocompetent patients, TA-GVHD usually arises where there is HLA haplotype sharing as occurs within families i.e. recipients of blood from relatives. The use of fresh blood, containing a large number of viable lymphocytes, is a further risk factor.

9 .1 Effect of leucodepletion on risk of TA-GVHD

In the first 3 years (1996-1999) of the UK Serious Hazards of Transfusion (SHOT) adverse reporting system, there were 12 reports of TA-GVHD, all fatal.[22-24] In the 6 years (2000-2005) since the implementation of universal leucodepletion of blood components (Nov 1999 in the UK), there has been only one reported case of TA-GVHD in a patient who did receive leucodepleted RBCs.[25,26,128,163] It is likely that leucodepletion does reduce the risk but does not eliminate it. At present gamma irradiation of blood components is the only accepted method to prevent TA-GVHD as it abrogates the proliferative capability of white cells in the units.

9 . 2 Risk of TA-GVHD in preterm infants

Newborns, particularly those who are of low birth weight and preterm, are considered to be at increased risk of TA-GVHD. However the magnitude of the risk and the requirement to transfuse irradiated cellular blood components are controversial issues for which no irrefutable, scientifically proven answers exist.[90] Although newborns especially very low birth preterm infants are immunodeficient when compared to older children and adults, very few cases of TA-GVHD have ever been reported in these patients. An extensive review by Strauss (2000)[90]

of reports, published in English, of infants in whom TA-GVHD developed within the first year of life, recorded 73 cases with only 5 of the 73 episodes occurring outside of the recognised risk factors for TA-GVHD:

Table 6 Fatal TA-GVHD in infants during first year of life

Underlying Medical condition Reported	Number
Primary Immunodeficiency disease	27
Related blood donor	26
Intrauterine and exchange transfusion	5
Exchange transfusion only	9
Aplastic Anaemia	1
No acknowledged risk factor	5

Thus, despite years of experience with thousands of transfused infants, unexpected TA-GVHD during infancy is rare. However TA-GVHD is always fatal and the presence of an underlying primary immunodeficiency disorder may not be apparent shortly after birth, when a transfusion is needed.[90] In the first UK SHOT Annual Report (1996-1997), a premature infant, born at 32 weeks and multiply transfused with non-irradiated RBCs over the next month, developed GVHD.[22] Investigations revealed an HLA-haplotype share between the infant and one of the red cell donors, and also that the infant was probably suffering from a rare form of severe combined immunodeficiency disease.

9.3 The effect of irradiation on red blood cells

During storage of y-irradiated RBCs, potassium leaks into the extracellular fluid and, within a few days, the concentration reaches a plateau level of approximately double the level in nonirradiated units: 70meq/l, with a range of 55-100mEq/l, depending on the storage solution and the quantity of extracellular fluid.[90] A case of hyperkalaemia-induced cardiac arrest occurred in a 62 day old baby girl following the rapid infusion through a central line of 120 mls of 6 day old red cells which had been irradiated 48 hours previously.[92] Although the dose of potassium infused with each small-volume RBC transfusion is small, the high concentrations in the primary unit can be quite dangerous for large volume transfusions which is why irradiated blood for exchange transfusion has a shelf-life of only 24 hours.

In this country and in the UK, irradiated red cells have a 14-day shelf life. If all pedipacks were irradiated by the IBTS before issue to hospitals, this would mean that assigned pedipacks to infants could only be used up to 14 days instead of the current 35 days. The result would be to increase donor exposure. The ideal would be to irradiate each individual pedipack immediately before transfusion. Many hospital blood banks in the US have irradiators and hence routine irradiation of all cellular components for neonates is easily implemented. However in this country access to a blood irradiator is limited to the IBTS at the NBC and the Munster Centre. Only one hospital blood bank in the country has an irradiator on-site.

9.4 Recommendations for the gamma-irradiation of cellular blood components to reduce the risk of TA-GVHD in the fetus and neonate: These guidelines are largely based on the guidelines published by the BCSH (1996a).[164]

- Donations from family members:

  All transfusions (red cell, platelets and granulocytes) from first or second degree relatives must be irradiated *(level III evidence, grade B recommendation).*

- Intrauterine transfusion (IUT):

  All blood, (RBCs or platelets) for intrauterine transfusion must be irradiated *(level III evidence, grade B recommendation).*

- IUT and subsequent exchange transfusion (ET) or 'top-up' transfusion:

  Blood for ET or 'top-up' transfusion must be irradiated if there has been a previous IUT of RBCs or platelets *(level III evidence, grade B recommendation).*

- Exchange transfusion:

  For other exchange transfusions irradiation is advisable provided this does not unduly delay transfusion. Blood for IUT and exchange transfusion must be transfused within 24 hours of irradiation *(level III evidence, grade B recommendation).*

- Top-up transfusions:

  The UK BCSH Guideline does not require irradiation for routine top-up transfusions of preterm or term infants unless there has been a previous intrauterine transfusion of RBCs or platelets, or unless the infant is in another 'at risk' group in which case irradiated pedipacks are recommended which at after irradiation will only have a 14 day shelf-life.

- When a child has a proven or suspected immunodeficiency (e.g. severe combined immunodeficiency):

  All transfusions (red cell, platelets and granulocytes) must be irradiated *(level III evidence, grade B recommendation)*

- Platelet transfusions:

  Platelet transfusions in utero for alloimmmune thrombocytopenia must be irradiated and all platelet transfusions given after birth to infants who have received red cells or platelets in utero must be irradiated. The IBTS now irradiates all platelets for neonatal use as irradiation has no effect on product. We recommend that all platelets for infants in the first year of life should be irradiated.

- Granulocyte transfusions:

  All granulocyte transfusions must be irradiated and transfused as soon as possible after irradiation *(level III evidence, grade B recommendation).*

- Cardiac surgery:

  There is no need to irradiate red cells or platelets for infants undergoing cardiac surgery unless clinical or laboratory features suggest co-existing immunodeficiency but there needs to be a high index of suspicion.[164] If in doubt, cellular blood components should be irradiated. It is increasingly recognized that infants with a variety of congenital cardiac lesions have lesions of chromosome 22, i.e. are variants of Di George's syndrome.[51] Dysmorphic infants with truncus or interrupted aortic arch who do not have all the features of Di George's syndrome and who need cardiac surgery should have irradiated blood until the syndrome has been excluded.[51] *(grade C recommendation).*

Section 10 Fresh Frozen Plasma/SD-Plasma

The clotting times of normal infant blood are longer than those of adults; those of premature infants (with reduced synthesis of clotting proteins by the liver) may be even longer but on its own is not an indication for plasma.

In the sick, usually preterm infant, bleeding is most often caused by DIC (secondary to perinatal asphyxia, NEC, sepsis) or liver disease.[117]

In an otherwise well infant, the commonest causes of bleeding are: neonatal alloimmune thrombocytopenia (see above section 8.5), vitamin K deficiency (haemorrhagic disease of the newborn), and inherited deficiencies of clotting factors, particularly haemophilia.[117]

10.1 Neonates with coagulopathy and bleeding

FFP/SD-Plasma is indicated for sick, usually preterm infants with significant coagulopathy and bleeding, often secondary to hypoxia, hypotension, sepsis or liver disorders or in infants who are at risk of bleeding from an invasive procedure because of significant coagulopathy.[165] A dose of 15ml/kg of FFP as well as a dose of vitamin K is recommended.[165] *(level IV evidence, grade C recommendation).* FFP at a similar dose is required to treat or prevent haemostatic failure associated with major blood loss and massive transfusion in infants, particularly if RBCs in SAG-M are being transfused (section 4.4 acute blood loss).

Responses should be monitored, as they will serve as a guide to further supportive care. The clinical response in a bleeding patient as well as the correction of abnormal coagulation parameters should be recorded.

A randomised controlled trial of prophylactic early FFP in preterm infants to prevent periventricular haemorrhage (PVH) had no effect on the risk of death or disability in babies born more than 8 weeks before term.[166]

- Routine administration of FFP to prevent PVH in preterm babies is not indicated.[166] *(1b evidence, grade A recommendation).*
- FFP should never be used as a simple volume replacement in babies *(grade A recommendation).*

10.2 Haemorrhagic disease of the newborn (HDN)

Newborn infants have moderately decreased levels of vitamin-K dependent clotting factors (Factors II, VII, IX and X), most marked between 2 and 7 days of age. This physiological deficiency can be exacerbated by breast feeding, prematurity, and liver disease leading to haemorrhagic disease of the newborn.[117]
Prophylactic vitamin K (single intramuscular dose) is routinely administered to all babies in this country immediately after birth to prevent this disease which classically presents at 2-7 days of age in babies who have not received prophylactic vitamin K at birth.
Early HDN presenting with severe haemorrhage within 24 h of birth is caused by severe vitamin K deficiency in utero as a result of maternal medication that interferes with vitamin K, e.g. anticonvulsants, antituberculous therapy and oral anticoagulants.[117] Prevention of early HDN is by a single injection of vitamin K at birth and antenatal administration of oral vitamin K to the mother during the last 4 weeks of pregnancy.[117]
Late HDN, 2-8 weeks after birth, can occur in breast-fed babies or infants with liver disease. Late HDN can be prevented in the healthy breast-fed baby by the single prophylactic intramuscular dose of vitamin K; babies with chronic liver disease or malabsorption require prolonged vitamin K supplementation.[117]
Clotting studies in HDN show a prolonged PT with normal platelets and fibrinogen, although the APTT may also be prolonged in severe deficiency.
HDN should be treated by vitamin K (1 mg) intravenously and also FFP or SD-Plasma (10-20 ml/kg) when there is significant bleeding.

10.3 Inherited deficiencies of clotting factors

Patients with inherited deficiencies of clotting factors may present in the newborn period and should always be managed in association with a specialised centre. Treatment or prevention of bleeding is with replacement of the deficient factor with specific factor concentrates. Recombinant factors, when available, are preferred to plasma-derived products. There are no single factor concentrates available for factors II, V and X. Plasma is used for factor V replacement. Prothrombin complex concentrates containing II, IX and X are used for factor II and X deficiencies.

10.4 FFP/SD-Plasma and ABO compatibility

FFP or SD Plasma must be ABO compatible with the recipient. FFP for infants provided by the IBTS has to be low titre for haemolysins and for many years has been from AB plasma, since this contains neither anti-A nor anti-B. Because of the risk of vCJD, a US sourced, pooled plasma, virally inactivated by the solvent detergent process, called SD-Plasma, is imported for use for all patients including neonates and may contain anti-A or anti-B haemolysins. Group O FFP or SD- Plasma must only be given to group O recipients. Infants or neonates who are not group O may be particularly susceptible to haemolysis from group O FFP because of the relatively high volumes required[165] *(level II1 evidence, grade B recommendation).*

Table 7 Principles of selection of FFP or SD-Plasma according to donor and recipient ABO blood groups in infants.

	Compatible ABO Group of Donor Plasma	
Infant ABO group	**FFP**	**SD-Plasma**
O	O, A ,B, AB	O, A, B, Uniplas*
A	A, AB	A, Uniplas*
B	B, AB	B, Uniplas*
AB	AB	Uniplas*

**Uniplas is a blend of A, B and AB plasmas with low titres of anti-A and anti-B, intended for use as a universal plasma, but used by the IBTS primarily for issue to AB patients. At time of writing, this is not a licensed product in Ireland.*

FFP and SD-Plasma of any Rh type may be given regardless of the Rh status of the recipient. No anti-D prophylaxis is required if Rh D-negative patients receive Rh D-positive FFP.[165,18] *(level II a evidence, grade B recommendation)*
A standard 180-micron blood filter is used for transfusion. An 80-micron filter can be used for small-volume transfusions.

SD-Plasma is a new product and adverse reactions should be reported to the National Haemovigilance Office at the National Blood Centre.

Section 11 Cryoprecipitate

Cryoprecipitate is prepared by the controlled thawing of a unit of FFP at 1 to 6^{0}C. Cryoprecipitate is a concentrated source of fibrinogen, Factor VIII and Factor XIII in a volume of 10 to 15 ml. Despite its high levels of Factor VIII, cryoprecipitate is not the product of choice for treating haemophilia; recombinant or virus-inactivated products remain first-line treatment. Likewise, patients with VonWillebrand's disease should be treated with pharmacologic agents (e.g., DDAVP) or virus-inactivated factor concentrates.

The most common use for cryoprecipitate is to restore fibrinogen

levels in patients with acquired hypofibrinogenaemia as occurs in DIC and massive transfusion. The small volume allows more rapid replacement particularly of fibrinogen than with FFP.
A dose of 1 to 2 units/10 kg raises a small child's fibrinogen level about 0.6 to 1 g/L. In infants, a single unit of cryoprecipitate as a standard dose is usually sufficient to achieve haemostasis.[94]

Neonates should be given only ABO-compatible cryoprecipitate; the cryoprecipitate suitable for neonatal use supplied by the IBTS is group AB. A standard 180-micron blood filter is used for transfusion; an 80-micron filter may be used for small-volume transfusion of single units.

Section 12 T Activation

The red cell T-antigen is a crypt antigen present on all human erythrocytes but expressed only after the removal of N-acetyl-neuraminic acid following exposure to neuraminidase.[167] Neuraminidase is produced by a variety of organisms, in particular streptococcus, pneumococcus, clostridia and bacteroides. Anti-T is an IgM antibody present in the plasma of almost all adults but is not present in the plasma of infants until about 6 months of life. It has been postulated that this ubiquitous antibody directed against the T antigen may be associated with haemolysis in patients whose red cells are activated e.g. infants with necrotising enterocolitis (NEC).
The clinical importance of T activation in relation to transfusion policies in neonatal medicine is unclear. Debate regarding appropriate transfusion management centres on whether transfusing plasma actually causes haemolysis.
A prospective observational study was carried out to examine the occurrence of T- and T-variant activated RBCs in a neonatal intensive care population involving over 2000 samples from 375 neonates and to investigate the occurrence of T-activation-associated haemolysis following transfusion.[168] It was found that 48 of 375 infants (12.8%) developed T-or T-variant-activated RBCs of whom 27% developed at least one episode of sepsis and 19% developed NEC. T activation was not always temporally associated with the onset of NEC or sepsis. Only 3 of 375 infants (0.8%) developed haemolysis; 2 had NEC and one E.Coli septicaemia; the haemolysis was associated with DIC and occurred before receiving any blood component. It is noteworthy that only a single infant had classical T activation, the remaining 98% of babies had T variant activation of their RBCs. Donor samples contained T but not T variant antibodies. The remaining 26 of 48 (54%) with T activation were healthy infants. 48% of infants with T-activated RBCs received significant amounts of standard blood components, but no transfusion-associated haemolysis occurred.[168] The routine screening for T activation of infants with sepsis or NEC is not justified and the provision of specially prepared blood components for infants with NEC is unnecessary. [168,169]
Any patient with NEC who develops haemolysis, should be investigated to determine the cause of this.[51] This should, where possible, include a lectin test to look for T-activation.[51]
The provision of low-titre anti-T components, such as washed RBCs, washed platelets and FFP low in anti-T is only warranted in the small proportion of infants in the setting of documented haemolysis clearly identified to have resulted from T activation,[169] or where there is a high suspicion of same; an exchange transfusion using low titre anti-T plasma and red cell products may be indicated [165] *(level IV evidence, grade C recommendation).*
Avoiding transfusion of plasma-containing blood components in infants with T-activated red cells in an attempt to prevent a potential risk of haemolysis may introduce a greater risk from neglecting the need for coagulation factors in critically ill infants requiring haemostasis support [165,169] *(level II / III evidence, grade B recommendation).*

Appendix 1

Key to levels of evidence and grades of recommendations in this guideline were derived from US Agency for Health Care Policy and Research

Evidence Levels

1a Evidence obtained from meta-analysis of randomised controlled trials.
1b Evidence obtained from at least one randomised controlled trial.
11a Evidence obtained from at least one well-designed controlled study without randomisation.
11b Evidence obtained from at least one other type of well-designed quasi-experimental study.
111 Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
1V Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of Recommendations

A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. *(Evidence levels 1a,1b).*
B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. *(Evidence levels 11a, 11b, 111).*
C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. *(Evidence level 1V).*

Appendix 2

MEMBERS OF THE NATIONAL BLOOD USERS GROUP

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