Red Blood Cell Transfusions in the Newborn

Recommendations of the Swiss Society of Neonatology

Elaborated by a working group of the Swiss Society of Neonatology consisting of (in alphabetical order): Romaine Arlettaz Mieth, Zurich; Laureline Barrielle, Lausanne; Inga Hegemann, Zurich; Gabriel Konetzny, Aarau; Christoph Rüegger, Zurich.

Editorial Responsibility: Christoph Rüegger

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1 Introduction

Red blood cell (RBC) transfusion is a frequently practiced medical intervention in neonatal intensive care, particularly when used as 'top-ups' for the recurrent correction of anaemia of prematurity.[1] Despite such frequent use, there has been little evidence in the past on which to guide the methods and indications for neonatal RBC transfusions on a local level of hospital laboratories and neonatal units. Since a number of studies and national guidelines have been published in this area over the recent years, the aim of the present guideline is to provide current evidence-based recommendations for the preparation, indication and administration of RBCs in newborns.

This guideline for newborns (up to 28 days of life) has been developed as a result of neonatal studies predominantly of very preterm (<32 weeks of gestational age) or very low birth weight (VLBW; <1.5 kg) infants. Since some of those infants will require transfusion beyond 28 days of life, this guideline addresses newborn infants of all gestational and postnatal ages (unless otherwise stated), although there is little evidence specifically related to term infants. Furthermore, these recommendations may not be appropriate for certain rare disorders (e.g., congenital heart disease) or unusual procedures such as extracorporeal membrane oxygenation.[2,3] In all cases, individual patient circumstances may dictate an alternative approach.

This guideline is divided into three sections: 1) how can we prevent or reduce neonatal RBC transfusions, 2) which laboratory processes must be considered before RBC transfusion, and 3), when and how should we administer RBCs to newborns? The literature published on these topics was reviewed using MEDLINE and the Cochrane Database of Systematic Reviews. Furthermore, information from other relevant international guidelines has been considered. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to

assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org/.

2 How can we prevent or reduce blood transfusions?

It is recommended that strategies be implemented to help reduce the need for RBC transfusions, particularly in preterm infants.[4] Iatrogenic phlebotomy loss resulting from the intensive clinical monitoring in the weeks immediately following birth remains the primary cause of neonatal anaemia. Strategies to limit iatrogenic blood loss in neonates include limited use of indwelling arterial lines, low volume blood collection technologies, use of non-invasive monitoring of blood gases and using blood cord samples rather than direct sampling from the neonate for RBC antibody screen and blood culture.

2.1 Delayed cord clamping

There is good evidence from trials to date that delayed cord clamping (60 to 180 seconds) increases haemoglobin levels at birth and improves iron stores in the first several months of life in term infants. In preterm infants, delayed cord clamping is associated with improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis (NEC) and intraventricular haemorrhage (IVH).[5]

Delayed cord clamping for 1 to 3 minutes for *term infants* and for at least 60 seconds for *preterm infants* is recommended to prevent iron deficiency and reduce the need for RBC transfusion.	
Strength of recommendation: strong	Level of evidence: high

2.2 Erythropoietin

In preterm infants, late administration of erythropoietin (EPO) between eight and 28 days after birth has been reported to reduce the number of RBC transfusions but not the total volume transfused per infant. A trend towards an increased risk of retinopathy of prematurity (ROP) has been described with late EPO.[6] Early EPO administration initiated before eight days after birth resulted in a small reduction in the number and volume of RBC transfusions. No significant difference in the rate of ROP was found, which has been a topic of concern in previous reviews.[7,8] Because of a high methodological and clinical heterogeneity among all studies on EPO use and limited clinical benefits identified to date, routine administration of EPO in preterm infants cannot be recommended.

In *preterm infants*, erythropoietin cannot be recommended to prevent anaemia and reduce RBC transfusions.	
Strength of recommendation: weak	Level of evidence: high

2.3 Iron supplementation

The available data suggest that infants who receive iron supplementation have a slightly higher haemoglobin level, improved iron stores and a lower risk of developing iron deficiency anaemia when compared with those who are not supplemented.[9] Therefore, international intake recommendations for enteral iron in preterm infants are 2 - 3 mg/kg/day (max. 5 mg/kg/d) from the age of 2 weeks until at least 6 months.[10] Higher iron doses (>5 mg/kg/day) are recommended for preterm infants during EPO treatment or after significant, uncompensated blood losses.

For *preterm infants,* enteral iron supplementation is recommended to lower the risk of developing iron deficiency anaemia.	
Strength of recommendation: strong	Level of evidence: high

3 Laboratory Section

3.1 What type of blood should we use?

3.1.1 Leucodepletion

All cellular blood products have to be leuco-depleted in Switzerland since 1999. Leucodepletion is a process for removing leucocytes from blood components by means of a special filter or by differential centrifugation.[11] There is good evidence to support the value of leucodepletion in preventing transfusion associated transmission of some infectious agents (Cytomegalovirus - CMV) and in reducing the risk of transfusion associated Graft versus Host disease (TA-GvHD – see section 4.3.2).[12]

Pre-storage leucodepletion of blood products significantly reduces the risk of CMV transmission for *all newborns*.	
Strength of recommendation: strong	Level of evidence: moderate

3.1.2 Irradiation

Irradiation (with 25 Gy gamma radiation) of cellular blood components is used to reduce the risk of TA-GvHD, a rare and usually lethal complication of transfusion of cellular blood products.

	Absolute indication	Relative indication
Foetus and neonate	– Intrauterine transfusion (IUT)[13] – Neonatal exchange transfusion (ET) – Top-up transfusions after previous IUT or ET for 6 months after the expected date of delivery.	– VLBW infants[14,15]
Immunodeficiency	– Known or suspected congenital cellular immunodeficiency	
Specific blood products	– Blood components donated by first or second-degree relatives.	

In the neonatal setting, irradiation of cellular blood products is recommended for intrauterine transfusions (IUT) and for donations from first- or second-degree relatives. For neonatal exchange transfusions (ET), irradiation is recommended provided this does not delay transfusion.[13] Irradiation of blood products for routine top-up transfusions of preterm or term infants is not generally recommended, unless there has been a previous IUT or ET, in which case irradiated components should be administered until 6 months after the expected date of delivery.[13] For hospitals with a dedicated on-site irradiator, irradiated blood products should be considered for VLBW neonates, since leucodepletion may be insufficient to eliminate the risk of TA-GvHD disease in these immunocompromised patients.[14,15]

Irradiation damages the RBC membrane, which increases the rate of potassium loss and the risk of hyperkalaemia, particularly after large-volume transfusions. Therefore, preferably fresh blood should be irradiated within 5 days after donation and transfused as soon as possible, ideally within 24 hours after irradiation.

All blood for intrauterine transfusion should be irradiated. For neonatal exchange transfusion, irradiation is recommended provided this does not delay transfusion. There is no general recommendation to irradiate blood for routine top-up transfusions of preterm or term infants. If a blood irradiator is located onsite, irradiated components should be administered to VLBW infants.	
Strength of recommendation: weak	Level of evidence: low

3.1.3 Cytomegalovirus

Guidelines for neonates vary widely and include recommendations both for and against routine use of CMV-seronegative products. With routine leucodepletion, the risk of CMV transmission from cellular blood products is low, whereas maternal breast milk represents a common source of infection. Therefore, CMV-seronegative products are generally not required in the routine clinical setting but may be

considered for large-volume intrauterine transfusions or for patients with severe combined immunodeficiency who are CMV negative.[11]

CMV-seronegative blood products are generally not required in routine clinical settings.	
Strength of recommendation: weak	Level of evidence: low

3.1.4 Washed RBCs

Cellular blood components may be modified by washing to reduce the level of residual substances (e.g., antibodies, serum proteins, additive solutions, potassium, cytokines) or to gain a haematocrit of 0.8 for intrauterine transfusions. For most small-volume transfusions, the risk of hyperkalaemia is extremely low, and the safety of additive solutions used for RBCs is established.[16]

For neonatal transfusions, routine washing of RBCs is not necessary.	
Strength of recommendation: weak	Level of evidence: low

3.1.5 Blood group

Red blood cell products should be compatible with the mother`s and infant`s ABO blood group after twofold testing. If a compatible blood group is not available, the universal donor blood type 0 Rhesus negative is recommended for neonatal transfusions. With this approach, a single blood unit can be used among multiple neonates with different ABO blood groups to reduce the risk of wastage.

Red blood cell products should be compatible with the mother`s and infant`s ABO blood group after twofold testing. Blood group 0 Rhesus negative is recommended as a universal donor type for neonatal transfusions	
Strength of recommendation: strong	Level of evidence: low

3.2 What do we know about storage, preparation and pre-transfusion testing?

3.2.1 Age of RBCs

Standard policy in most blood banks is to dispense the oldest RBC unit available. A systematic review with meta-analysis that included five trials in neonates reported no difference between transfusion with fresher versus older RBCs with regard to mortality and morbidity.[17] Therefore, fresh (<7 days) RBCs are not advocated for routine use but may be considered for large-volume transfusions (IUT or ET). For non-irradiated top-up transfusions, aliquots must be no more than 28 days since donation. When irradiation is conducted, blood should be transfused within 24 hours of irradiation and, in any case, by 5 days or less from collection.[18,19]

Fresh RBCs are not advocated for routine use. Non-irradiated aliquots for top-up transfusions can be stored for 28 days after donation. Irradiated blood products should be transfused within 24 hours of irradiation and within no more than 5 days from collection.

Strength of recommendation: strong	Level of evidence: high

3.2.2 Satellite units

Donor exposure can be reduced by fractioning a single donor unit into multiple smaller aliquots ('Paedipaks', approximately 50 mL) to be reserved for a single neonate for repetitive transfusions until expiry of the unit is reached. To avoid volume overload, Paedipaks are 'plasma reduced' and prepared to a haematocrit of 0.5 – 0.7.

Paedipaks should be used for all RBC to-up transfusions to minimise multiple donor exposure.	
Strength of recommendation: strong	Level of evidence: low

3.2.3 Time limit for RBC transfusion

It is important that blood components brought to room temperature are transfused as soon as possible (start at least within 30 minutes) following receipt from the blood bank. RBC transfusion should be completed within 4 hours following removal of the unit from a monitored blood refrigerator.

When removed from cooling, RBC transfusion should begin within 30 minutes and should be completed within 4 (-6) hours.	
Strength of recommendation: strong	Level of evidence: low

3.2.4 Pre-transfusion serologic testing

A pre-transfusion blood sample taken from the newborn (capillary, venous or arterial sample from the infant or the umbilical cord) is used by the blood bank to perform a 'type and screen' limited to ABO and Rhesus D typing of RBCs. Mother serum or plasma can be utilised in infants below 4 weeks of age to screen for unexpected RBC antibodies. If mother serum is unavailable, RBC antibody screening will be performed in a neonatal blood sample.[19] If a mother`s initial antibody screen and the infant`s direct antiglobulin (Coombs) test is negative, it is generally not necessary to repeat the screen up to four months of age. In case of a positive antibody screen in the mother or a positive direct antiglobulin test in the newborn, transfusion of antigen negative red cell units is possible with a negative cross match.

Pre-transfusion testing includes AB0 and D typing of RBCs (neonatal blood sample) and screening for RBC antibodies (maternal or neonatal blood sample).	
Strength of recommendation: strong	Level of evidence: low

3.3 Laboratory section - summary

RBCs for small-volume neonatal top-up transfusions	
Paedipaks	Splits (approximately 50 mL) of a single donation
Preparation	Leucodepleted, plasma-reduced (haematocrit 0.5 – 0.7)
Blood group	0, RhD negative or compatible to mother and child

Irradiation	Not necessary, consider for VLBW infants in hospitals with on-site irradiator. Irradiation within 5 days after donation
Time limits for transfusion	Within 24 hours after irradiation Within 4 hours after removal from the storage

4 Clinical section

4.1 When should we transfuse neonates?

Until recently, evidence on transfusion thresholds in preterm infants was limited. Several randomised controlled trials have now addressed the risks and benefits of liberal or restrictive RBC transfusion policies in VLBW infants. The PINT trial showed no difference between low and high haemoglobin transfusion thresholds with respect to clinically significant complications in neonates to 36 weeks of postmenstrual age.[20] However, post-hoc analyses suggested that cognitive impairment may be more common with restrictive transfusion thresholds.[21] The TOP and ETTNO trials further examined the effect of transfusion practice on neurodevelopment in extremely-low-birth-weight infants.[22,23] Both trials reported that a liberal versus restrictive RBC transfusion threshold did not impact the risk of death or disability (cognitive deficit, cerebral palsy or severe visual and hearing impairment) at 24 months corrected age. Of note, no effects of RBC transfusions on beneficial or adverse outcomes including stage 2 or 3 NEC, bronchopulmonary dysplasia, and ROP were found in the TOP and ETTNO trials.

To limit donor exposure and the risk of transfusion-related complications, we recommend restrictive RBC transfusion thresholds for newborn infants with anaemia. Although little evidence exists specifically related to term infants, we advocate for the use of the same transfusion thresholds for preterm and term infants without acute blood loss for reasons of practicability.

Restrictive thresholds for RBC transfusion are recommended for *newborn* infants without acute blood loss.	
Strength of recommendation: strong	Level of evidence: high

Commonly, RBC transfusion haematocrit trigger thresholds are based on the infant's postnatal age and current state of health (critical versus noncritical). In line with the restrictive policy of the ETTNO study protocol, we suggest the following RBC transfusion thresholds:

	Red blood cell transfusion threshold for newborn infants without acute blood loss	
	Critical health state[1] [Haematocrit (%) / Haemoglobin (g/dl)]	Noncritical health state (%) [Haematocrit (%) / Haemoglobin (g/dl)]
Day of life 0 - 7	<34 / 11.3	<28 / 9.3
Day of life 8 - 21	<30 / 10.0	<24 / 8.0

Day of life >21	<27 / 9.0	<21 / 7.0

[1]critical is defined as an infant having at least 1 of the following criteria:
- invasive mechanical ventilation
- CPAP or NIPPV with FiO_2 >0.25 for >12/24 hours
- treatment for patent ductus arteriosus
- acute sepsis
- necrotizing enterocolitis requiring inotropic/vasopressor support
- severe apnoea's requiring intervention despite caffeine use and CPAP

The need for transfusion in an infant with acute blood loss is dependent upon persistent clinical signs of inadequate oxygen delivery following intravascular volume restoration and may dictate an individualised approach.

4.2 How should we administer red blood cells?

4.2.1 Vascular access

RBCs can be transfused through most peripheral and central venous catheters. Although there is a complete lack of literature on the preferred vascular access, a separate peripheral venous access is generally preferred over the use of a central venous catheter because of lower risks for thrombosis, occlusion, dislodgment or infection.[24] Narrow lumen catheters, such as peripherally inserted central catheters (PICC lines) are not recommended for the transfusion of RBCs due to reduced flow rates with the accompanying risk of clotting, catheter obstruction, and haemolysis due to excessive pressures.[25,26]

A separate peripheral intravenous line is the preferred vascular access for RBC transfusions in newborns.	
Strength of recommendation: weak	Level of evidence: very low

4.2.2 Blood filter

Currently, there is no evidence to show whether the use of blood filters during neonatal RBC transfusion is beneficial. With the aim to remove cellular aggregates, cellular debris and clots potentially harmful to the newborn, most regulatory authorities recommend using blood administration sets appropriate for small volume transfusions containing an integral 170-260-micron filter.[27,28] Microaggregate filters are not indicated.

For RBC transfusions, a filter should be used to retain particles potentially harmful to the newborn.	
Strength of recommendation: weak	Level of evidence: very low

4.2.3 Transfusion volume

In general, small volume 'top-up' transfusions (traditionally 10-20 mL/kg, typically 15 mL/kg) are given to preterm infants in the context of anaemia of prematurity. However, there is limited evidence to define optimal volumes for neonatal RBC transfusion, particularly with regards to long-term outcomes.[29] Larger volumes maximise haemoglobin levels while minimizing numbers of transfusions required, but they may also increase the risk of transfusion associated volume overload in non-bleeding infants.[30,31] Thus, in view of data supporting restrictive transfusion thresholds for preterm infants, top-up transfusion volumes of 15mL/kg may be suggested. Larger volumes of >20mL/kg may be required in special situations such as haemorrhagic shock, severe anaemia, expected ongoing risk factors or concurrent bleeding.

A transfusion volume of 15 mL/kg is recommended for non-bleeding neonates in most cases.	
Strength of recommendation: weak	Level of evidence: very low

4.2.4 Transfusion rate

The appropriate rate of neonatal RBC transfusion may vary significantly according to the clinical circumstances. Slower transfusion rates decrease the risk of transfusion associated volume overload (e.g. in newborns with cardiac failure), whereas rapid transfusions may cause hyperkalaemia and haemodynamic disturbances, which have been described as a potential risk factor for IVH and persistent ductus arteriosus in VLBW infants.[32] In stable newborns, a transfusion rate of 5 mL/kg/h is commonly recommended to avoid such adverse outcomes and to complete transfusion within four hours of removal of the blood unit from a monitored blood refrigerator, as mentioned above (section 3.2.3).[33,34] Infants with active bleeding or haemorrhagic shock will require RBCs to be transfused as rapidly as possible. No data is available on the effect of transfusion rate on long-term neonatal outcome.

In stable newborns, an RBC transfusion rate of 5 mL/kg/h is recommended.	
Strength of recommendation: weak	Level of evidence: very low

4.2.5 Diuretics

Furosemide is sometimes used in transfused infants to prevent fluid overload. There is some evidence that a single dose of prophylactic furosemide (1mg/kg) may result in a small and clinically irrelevant reduction in oxygen requirement after transfusion.[35,36] Post-transfusion diuretics are not used routinely and should only be considered where there is clinical concern regarding significant fluid overload.

Furosemide before and after an RBC transfusion in preterm infants is not recommended.	
Strength of recommendation: weak	Level of evidence: low

4.2.6 Compatible intravenous fluids and co-administration of drugs

It is good clinical practice to avoid the co-administration of any intravenous fluid through the same line used for blood components. Solutions containing calcium (e.g., Ringer's lactate) antagonise citrate anticoagulant and may allow clots to form if mixed in the same infusion line.

Medicines must not be added to the blood unit. Whenever possible, intravenous drugs should be administered between transfusions or administered through a second venous access device (or the separate lumen of a multi-lumen central venous catheter). If this is not possible, the transfusion should be temporarily stopped, and the line flushed with 0.9% saline before and after administration of the drug.

Co-administration of intravenous fluids and drugs through the same line used for RBC transfusion should be avoided.	
Strength of recommendation: weak	Level of evidence: very low

4.3 What are the risks of RBC transfusions in neonates?

Blood transfusions are associated with both infectious (transfusion-transmitted infections) and non-infectious serious hazards of transfusion and with certain complications specific to neonates.[37,38]

Risks associated with RBC transfusions in neonates	
Immediate adverse effects	– Febrile non-haemolytic transfusion reactions – usually clinically mild. – Allergic transfusion reactions – ranging from mild urticaria to life-threatening angio-oedema or anaphylaxis. – Acute haemolytic transfusion reactions – e.g., ABO incompatibility. – Bacterial contamination of blood unit – range from mild reactions to rapidly lethal septic shock depending on species. – Transfusion-associated circulatory overload (TACO). – Transfusion-related acute lung injury (TRALI). – Hypothermia – Potassium effects
Delayed and long-term adverse effects	– Delayed haemolytic transfusion reactions (DHTRs) – Transfusion-associated graft-versus-host disease (TA-GvHD) – Iron accumulation

4.3.1 Immediate and severe life-threatening reactions

Acute haemolytic reactions: The majority of acute haemolytic reactions is caused by transfusion of ABO incompatible blood. Most haemolytic reactions are the results of human errors such as the transfusion of properly labelled blood to the wrong patient, or improper identification of pre-transfusion blood samples. In the neonate, an acute haemolytic event may be characterised by increased plasma free haemoglobin, haemoglobinuria, increased potassium concentration, decreased pH, and uncontrolled bleeding due to disseminated intravascular coagulation.[38] Management: stop transfusion, notify hospital blood bank and send a blood sample for work-up, initiate intensive care measures such as vigorous treatment of hypotension and maintenance of renal blood flow.

Bacterial contamination of blood unit: Although rare, this more often occurs with platelet components than with RBCs. Bacteria may be introduced into the pack at the time of blood collection from sources such as donor skin, donor bacteraemia or equipment used during blood collection or processing. Bacteria may multiply during storage. In neonates, early clinical signs of sepsis are unspecific, but septic shock can rapidly be fatal. Management: Supportive care, blood cultures from infant and blood unit, broad-spectrum antimicrobials.

Severe allergic (anaphylactic) reactions: They are characterised by cardiovascular instability including hypotension, tachycardia, cardiac arrhythmia, shock and cardiac arrest. Sometimes respiratory involvement with dyspnoea and stridor are prominent. In rare cases, patients with IgA deficiency who have anti-IgA antibodies can have anaphylactic reactions. Management: stop the transfusion, supportive care including airway management. Adrenaline, steroids and antihistamines as indicated.

Transfusion-related acute lung injury (TRALI): This is a clinical diagnosis of exclusion characterised by acute respiratory distress and bilaterally symmetrical pulmonary oedema with hypoxaemia developing within 2 to 8 hours after a transfusion. TRALI is thought to occur secondary to cytokines in the transfused product or from interaction between patient white cell antigens and donor antibodies (or vice versa). Management: symptomatic support for respiratory distress (non-invasive or endotracheal ventilation, oxygen). Symptoms generally resolve over 24-48 hours.

4.3.2 Delayed and long-term adverse effects of transfusion

Transfusion associated Graft Versus-Host Disease (Ta-GVHD): This rare and almost always fatal complication occurs when donor lymphocytes in a blood donation engraft in the patient and cause an immune response against the recipient's cells of a different HLA type. The donor lymphocytes damage target organs especially bone marrow, skin, liver and gastrointestinal tract. Neonates at risk include those who have congenital immunodeficiency syndromes, those who received intrauterine or exchange transfusions, and VLBW infants. Another reported setting for Ta-GVHD are immunocompetent recipients of blood from biologically related (directed) or HLA identical donors, where the transfused lymphocytes will not be eradicated by the host. The clinical syndrome comprises sepsis-like symptoms, skin rash, pancytopenia, abnormal liver function and diarrhoea. The usual onset of symptoms in infants is several days post transfusion. Gamma irradiation of cellular blood products effectively prevents TA-GVHD.

Delayed haemolytic transfusion reactions (DHTRs):

In DHTRs an antibody immune response occurs within 2 weeks (days 3-28) after transfusion or pregnancy. Antibodies to the Kidd blood group system are the most common and severe cause, followed by antibodies against Duffy, Kell or MNS antigens. They cause shortened red cell survival with clinical features of fever, jaundice and lower than expected haemoglobin following transfusion. Most delayed haemolytic reactions produce few symptoms and may go unrecognised. When an antibody is identified in the pre-transfusion antibody screen, appropriate antigen negative blood should be provided. Sometimes antibodies fall below detectable limits (especially Kidd) and may not be detected by pretransfusion testing.

4.4 Which monitoring is recommended during and after an RBC transfusion?

Infants receiving transfusion should be monitored for signs of potential complications of transfusion. Vital signs (temperature, pulse, respiratory rate, blood pressure, oxygen saturations) should be measured and recorded at the following timepoints:

- before the start of each transfusion
- 15 minutes after commencement of each pack
- hourly until conclusion at the completion of transfusion
- 4-hourly in the 24 hours following transfusion

4.5 Which immediate management of a suspected transfusion reaction is required?

Consider possible transfusion reaction where there is a change or deterioration in the infant's condition.

1. Stop the transfusion if a transfusion reaction is suspected
2. Check vital signs

3. Maintain IV access using a new giving set and 0.9% sodium chloride
4. Check the right blood unit has been given to the right patient
5. Treat the patient as required
6. Notify blood bank and treating medical team
7. Take a blood sample (from a different vein) for blood group serology, full blood count and serum biochemistry.
8. Consider need for blood cultures if sepsis suspected. Blood gases if respiratory distress present. Urine check for haemoglobinuria. Coagulation screen if bleeding.
9. Parents of neonate are to be informed.

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