

A practical guide to red blood cell transfusion in children

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Abstract

Red cell transfusion is common in paediatric practice and indicated in haemorrhagic shock, anaemia and certain inherited haematological diseases. As with other blood products there are risks associated with their administration and improper use. Extensive guidance is available in the UK in order to maintain adequate haemovigilance and safe transfusion practice. This article summarises the rationale behind red cell transfusion and offers a practical guide to clinical decision making in the acute hospital setting.

Keywords anaemia; blood transfusion; haematology; haemorrhage; red blood cell

Introduction

Allogenic red blood cell transfusions are a part of everyday practice across the paediatric specialities in the acute hospital setting and can be lifesaving when used appropriately. The most commonly transfused groups are children on paediatric or neonatal intensive care units (PICU/NICUs), those undergoing cardiac surgery, transfusion-dependent children with inherited conditions and those requiring intensive chemotherapy for malignant disease. Comprehensive safe transfusion guidance in the UK is provided by the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC; see the Handbook of Transfusion Medicine, 5th edition and the Guidelines for the Blood Transfusion Services in the UK, 8th edition), NHS Blood and Transfusion and National Institute for Health and Care Excellence (NICE) guidance (Blood Transfusion, 2015; ng24). These national guidelines alongside local hospital based policies reflect the inherent risks and complications of transfusing blood products.

Recent studies suggest that a significant percentage of paediatric transfusion recipients receive only one transfusion during

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their admission raising the possibility that some may be avoidable. Given the finite supply of red cell donors in the UK clinicians must judiciously transfuse red cells and other blood products in order to avoid wasteful use of such a valuable resource.

Leaning on local and national guidance is key to haemovigilance but may leave you unclear about the rationale behind transfusion practice. This article aims to guide you through the why, when and how of red cell transfusion in paediatrics. Armed with this information you may better understand how to treat your individual patient and anticipate potential complications.

Red blood cell physiology

Red blood cells, or erythrocytes, make up around 45% of whole blood and 99% of its cellular components, with the remainder consisting of white blood cells and platelets. Circulating blood volumes vary with age but as a guide are approximately 90ml/kg for term infants under 3 months, 80ml/kg for older infants and children and 70ml/kg for adolescents. For simplicity a figure of 80ml/kg could be applied across all ages. Red cells consist of the oxygen carrying proteins haemoglobin made up as four protein subunits and a central haem moiety (an iron containing molecule). Haemoglobin acts as a store for oxygen feeding the dissolved oxygen that is available to the tissues.

Normal haemoglobin (Hb) values vary with age as well as sex, race and ethnicity. From birth to three months of age infants develop a physiological anaemia with high Hb levels of >140 g/L in health term infants at birth which drop to a nadir of around 110 g/L at six to nine weeks of age. For older children the mean Hb sits at around 130 g/L. The World Health Organisation define anaemia as Hb values below 115 g/L in children and severe anaemia if less than 80 g/L.

It makes sense therefore that the transfusion of red blood cells increases overall circulating blood volume and to an extent systemic oxygenation. However this does not necessarily translate to improved oxygen delivery, particularly to peripheral vascular beds. Additionally the affinity haemoglobin has for oxygen is determined by factors associated with tissue activity. As described by oxygen-haemoglobin dissociation curve increased body temperature, acidosis, hypercarbia and increase DPG (2,3-diphosphoglycerate - a by-product of glycolysis) cause oxygen to dissociate from haemoglobin at a higher pO₂ than normal. This means that in active tissues oxygen can be delivered more readily.

Pre-transfusion testing and safe transfusion practice

Blood transfusion is a complex, high risk, multi-step procedure that relies on collaborative team working and strict adherence to well described procedures in order to minimise errors and adverse outcomes.

Following blood donation, in addition to blood grouping and antibody screening, the following mandatory tests are performed:

- Hepatitis B – HBsAg
- Human immunodeficiency virus – anti-HIV 1 and 2 and HIV NAT (nucleic acid testing)
- Hepatitis C – anti-HCV and HCV NAT
- Human T-cell lymphotropic virus – anti-HTLV I and II
- Syphilis – syphilis antibodies

Additional tests, performed in special circumstances, include:

- Malarial antibodies
- West Nile Virus antibodies
- *Trypanosoma cruzi* antibodies

Once blood is processed and tested it can be refrigerated and stored for up to 42 days.

Label samples carefully and get them checked before sending to the laboratory

At the point of requesting red cells for transfusion strict sample labelling policies are in place in order to minimise the risk of administering the wrong blood into patients. Blood transfusion services have a 'zero tolerance' policy with incorrectly labelled samples so ensure that requests are second checked to mitigate this risk. Other than in the emergency setting, where O D-negative blood is used, red cell transfusions should be fully cross-matched and only compatible products given.

Gain consent and document

Prior to administering red cells clinicians should obtain 'valid consent' which must be documented in the clinical records. Signed consent is not typically mandatory but may be a local requirement. Information leaflets for parents and children are available from the UK Transfusion Service. Where emergency treatment is necessary seeking consent must not delay or prevent transfusion and information must be given to the family retrospectively. Although rare in paediatric practice it is important to be aware of management strategies in the case of parents or their child refusing transfusion of blood components and products for religious or cultural reasons. For example Jehovah's Witnesses will not accept transfusions of whole blood or its major derivatives. Such a family may wish to involve the hospital liaison committee to give support in these circumstances. These can be very challenging clinical encounters and so local advice should be sought. Crucially one must respect the family's wishes and work with them to find an agreeable solution. In the emergency situation the legal position is that in the unconscious patient whose wishes regarding blood transfusions may be unknown, the doctor caring for the patient is expected to act on the basis of what is known of the patient's wishes, what is clinically necessary, and what is in the best interests of the patient.

Most transfusion incidents are avoidable

The UK Serious Hazards of Transfusion (SHOT) data revealed that the majority of transfusion incidents are preventable and nearly always caused by human error. JPAC recommend following the 'transfusion ten commandments' in order to ensure safe transfusion practice.

In essence they start by asking 'is blood transfusion necessary in this patient?' followed by ensuring that the 'right blood' is given to the 'right patient' at the 'right time' in the 'right place' (see JPAC, Handbook of Transfusion Medicine, 5th edition for full details).

When 'special requirements' are indicated

When requesting red cells one must consider if 'special requirements' are indicated for their patient. These include CMV negative and irradiated products.

CMV-negative blood

Cytomegalovirus (CMV) is a common herpes virus that causes asymptomatic infection or mild feverish illness in healthy immunocompetent children. The virus persists in blood monocytes in up to 60% of adults, including blood donors, who are lifelong carriers of the virus, meaning that CMV positivity in transfused blood is very common. CMV infection can cause severe, occasionally fatal infection in neonates and immunocompromised children and so 'CMV negative' blood is only recommended for the following patient groups:

- Intrauterine transfusion
- Neonates up to 28 days post expected date of delivery
- Allogenic haematopoietic stem cell transplant recipients
- During pregnancy (to protect the fetus)

NB. Organ transplant patients do *not* require CMV negative blood.

Irradiated blood

Following variant Creutzfeldt–Jakob disease (vCJD) risk-reduction measures introduced in 1999 donor blood has universally undergone leucodepletion. This process involves filtering the blood to remove white cells. Despite this certain patient groups require irradiated blood products in order to prevent donor white blood cells replicating and mounting an immune response manifested as transfusion-associated graft-versus host disease (TA-GvHD). Irradiated blood products are treated with either gamma or x-rays. Indications for irradiated blood include:

- Haemato-oncology patients - depending upon the disease and type of immunosuppressive drugs and biologicals - examples include:
 - Acute leukaemia if receiving donations from first or second degree relatives
 - Hodgkin's lymphoma
 - 7 days before stem cell harvest
 - Those treated with purine analogues and certain monoclonal antibody therapy

We recommend that you consult with local policies as they may vary from the above.

When to transfuse: transfusion thresholds

In the acute hospital setting decision making around when to transfuse can be difficult particularly given the known associated risks and complications. Broadly speaking red cell transfusion triggers fall into two groups - haemorrhage shock and anaemia.

Haemorrhagic shock

WHO define clinically significant bleeding according to adult grades which have been pragmatically modified for paediatric practice. There is little direct evidence to guide practice in children. Massive blood loss is defined as either 80ml/kg (i.e. entire circulating volume) in 24 hours or 40ml/kg in 3 hours. Practically speaking however accurate measurement of blood loss is very difficult and so evidence or suspicion of serious haemorrhage with accompanied haemodynamic changes expected with hypovolaemia are the usual triggers. Blood loss may be obvious as in trauma but may also be occult, caused by surgery or other procedures.

Non-infectious transfusion reactions

	Description and mechanism	Onset	Severity	Treatment
Acute haemolytic transfusion reaction (AHTR)	From ABO incompatibility leading to rapid onset haemolysis, release of inflammatory cytokines, circulatory shock, acute renal failure and coagulopathy	Sudden	Life threatening	Aggressive fluid replacement and diuresis
Delayed AHTR	Haemolysis of transfused cells in patient already 'alloimmunised' to a red cell antigen by blood transfusion or pregnancy; most common are Kidd and Rh antigen	More than 24 hours after transfusion - up to 14 days; need to confirm diagnosis with laboratory investigations	Moderate - falling Hb concentration, jaundice and fever to Haemoglobinuria and acute renal failure	Supportive
Febrile non-HTR	More common with platelets - release of cytokines from leucocytes, fever ± rigors, myalgia and nausea in absence of other symptoms	Within 2 hours - must be a diagnosis of exclusion	Mild	Slowing or temporarily stopping infusion, antipyretics - if symptoms worsen stop and consider haemolytic or bacterial reaction
Allergic reactions	More common with platelets and FFP (as plasma rich), range from mild urticaria to life threatening anaphylaxis. Following British Society for Haematology guideline investigations	Sudden, may occur in IgA-deficient individuals	Can be mild to life threatening angio-oedema or anaphylaxis	Antihistamines if mild, if severe stop infusion, resuscitation measures as per APLS guidance, early IM Adrenaline
Transfusion-associated lung injury (TRALI)	1:150,000 units transfused; Donor blood antibodies react with patient's neutrophils, monocytes and pulmonary endothelium, particularly if multiple donors	Within 2–6 hours - fever, rigors, breathlessness, cough, hypotension, chest X-ray - bilateral nodular shadowing	Life threatening	Supportive oxygen therapy, may include mechanical ventilation
Transfusion-associated circulatory overload (TACO)	Acute or worsening pulmonary oedema due to volume excess	Within 6 hours, high risk in those with underlying cardiovascular disease	Life threatening	Supplementary oxygen and diuretics ± mechanical ventilation
Hypotensive reactions	Isolated fall in systolic blood pressure of >30 mmHg, no evidence of allergic reaction or haemorrhage	Within 1 hour	Most transient, can progress to shock or organ dysfunction	Stop infusion, nurse patient flat with leg elevation
Transfusion-associated graft-versus-host disease (Ta-GvHD)	Rare; viable lymphocytes in donated blood engraft in patient and mount immune response against recipient cells of different HLA type, typically patients with immunodeficiency or undergoing chemotherapy	7–14 days (up to 30 days)	Almost always fatal	Preventative strategy - standard leucodepletion as well as irradiating red cells

Table 1

Transfusion-transmitted infections

Bacteria-associated sepsis	Mild pyrexia to rapidly lethal septic shock; rare, more common with platelets (as stored at higher temperature); sudden onset; if highly pathogenic bacteria then can be life threatening acute severe reaction; treatment includes broad-spectrum antibiotics, haemodynamic support.
Syphilis	Donations all screened. No reported cases of transmission since surveillance began in 1996.
Hepatitis A, B, C & E	Hepatitis A and E are spread by the faeco-oral route (usually contaminated food and water) and transmission by blood transfusion is very rare. Blood is not screened for either virus. Hepatitis B and C are transmitted by infectious blood and bodily fluids with the former remaining the most common viral transfusion-transmitted infection - with <1 in 1.2 million donations for HBV and <1 in 28 million for HCV.
Cytomegalovirus (CMV)	Common virus that causes asymptomatic infection or mild glandular-fever like illness in most healthy patients. 50–60% of UK adults in the UK are lifelong carriers. Can cause severe, sometime fatal, infection in fetuses, neonates and immunocompromised patients (see - when 'special requirements' are indicated - above).
Human immunodeficiency virus (HIV) 1 & 2	Transmission was common during the 1980's epidemic but with modern donor selection and HIV RNA screening it is now rare in the UK - <1 in 7 million donation.
Human T-cell lymphotropic virus types I and II	HTLV I associated with 1–4% lifetime risk of developing adult T-cell leukaemia/lymphoma; clinical significance of HTLV II is unknown. Both virtually eliminated by leucodepletion of blood products in UK.
Human parvovirus B19	Transmission is very rare. The virus is resistant to routine solvent detergent treatment. Infection is typically asymptomatic without any chronic carrier state.
West Nile virus	Transmission is very rare as donors returning from effected areas are deferred from donation for 28 days.
Dengue/Zika/CHIKV	UK practice is to delay donation for a minimum of 6 months for individuals returning from tropical virus risk endemic areas.
Malaria	Very rare in UK despite increasing international travel.
Chagas	Serious multi-system disease endemic in Central and South America. No reported cases of transmission in the UK.
Variant Creutzfeldt–Jakob disease (vCJD)	Four cases of transfusion-transmitted infection reported prior to the risk reduction measures introduced in 1999. These included leucodepletion of all blood components. Currently there is no practical screening test for blood donors.

Table 2

The clinical priorities are early recognition of significant bleeding and instigation of resuscitation and control of ongoing bleeding. In trauma this may be damage control resuscitation (e.g. applying tourniquets or pelvic splints) prior to definitive surgical repair or interventional radiology. With ongoing bleeding early activation of the local hospital massive haemorrhage protocol will result in rapid provision of O D-negative or group specific red cells. As per the Acute Paediatric Life Support guidelines initial red cell transfusions should be given as 5ml/kg aliquots of warmed packed red cells. All transfused blood products should be prescribed in ml/kg for children weighing less than 50kg.

Following red cell transfusion one should anticipate and treat coagulopathy and thrombocytopenia. A ratio of at least 1 Fresh Frozen Plasma (FFP):2 red cells: 1 platelets is recommended. In addition to blood products the RCPCH recommend that Tranexamic acid (TXA; 15mg/kg over 10 minutes followed by 2mg/kg/hr) should be given as an antifibrinolytic agent until bleeding is controlled. This advice followed the publication of the CRASH-2 trial published in 2010 which demonstrated reduced mortality in adult trauma. Finally in order to optimise cardiac function, perfusion and oxygenation clinicians must aim to avoid acidosis, hypothermia, hypocalcaemia and hyperkalaemia.

Anaemia

Decision making is often based pragmatically on Hb levels which is a surrogate marker for clinical transfusion need. Anaemia may be caused by one of three broad mechanisms; reduced red cell production, increased red cell destruction or blood loss (as detailed above). Reduced production is typically as a result of inhibition or inefficient stimulation of haematopoiesis (by proinflammatory cytokines for example) and inadequate supply of vitamin B12 or iron. Increased destruction may be caused by haemolysis or reduced red cell life span (e.g. phagocytosis or splenic removal from the circulation).

Evidence over the last 20 years has consistently demonstrated that a more restrictive use of red cells is at least equivalent to or maybe even superior to maintaining high Hb levels using liberal administration of donor blood. The exception to this is in the context of extreme anaemia (Hb < 50 g/L) where English et al. showed a significantly increased risk of mortality in malarial children in Kenya. The first of three landmark papers over the last two decades was the Transfusion Requirement in Critical Care (TRICC) trial published in 1999 which showed that using a transfusion threshold 70 g/L reduced the number of transfusions received by euvolaemic, non-haemorrhaging critical ill adults without worsening outcomes. Subsequently the TRIPICU (Transfusion strategies for patients in paediatric intensive care units) randomised trial by Lacroix et al., in 2007 similarly showed that a restrictive Hb transfusion trigger of 70 g/L was as safe as a liberal Hb trigger of 95 g/L and was associated with reduced blood use. Furthermore the development of multi-organ dysfunction syndrome was not significantly difference between the two groups. It remains unclear however if this can be extrapolated to unstable patients. They stated that a higher threshold should be considered if the child has symptomatic anaemia or impaired cardiorespiratory function.

The most recent comprehensive guidance was published in the *British Journal of Haematology* in 2016. The guidelines on

transfusion for fetuses, neonates and older children similarly recommends the use of a Hb threshold of 70 g/L in stable non-cyanotic patients. For unstable patients or symptomatic anaemia a higher threshold may be considered. The Premature Infants in Need of Transfusion (PINT) trial in 2006 demonstrated similar findings amongst neonates. It is reasonable to conclude that in haemodynamically stable, acyanotic children a transfusion threshold of 70 g/L should be adopted.

Another group of patients who may require more frequent red cell transfusions are children with haematological disease such as beta thalassaemia major or sickle cell disease. Children with sickle cell disease require transfusions to maintain levels of HbS <30% and as secondary prevention of recurrent strokes and in young children with recurrent chest syndrome for example. Children with rare inherited causes of anaemia including unstable haemoglobins and Diamond Blackfan anaemia also require regular transfusions.

Currently transfusion guidelines differ from the recommendations described in larger clinical trials. Transfusion volumes for non-bleeding infants and children, excluding those on chronic transfusion programmes, should generally be calculated to take the post-transfusion Hb to no more than 20 g/L above the transfusion threshold. In children over 50kg (as in adults) NICE recommend transfusion of a single unit of red cells in non-bleeding patients. For children under 50kg there is no current evidence based ideal Hb, a target of Hb is 120 g/L is reasonable, but should not exceed 140 g/L. Volume transfused should be minimised for infants and children taking into account the likelihood of requiring subsequent transfusions and should not exceed 20ml/kg for top-up transfusions.

Typical transfusion volumes are calculated using the equation.

$$\text{Transfusion volume} = \frac{\text{weight(kg)} \times \text{desired increment in Hb} \left(\frac{\text{g}}{\text{L}}\right) \times \text{transfusion factor}}{10}$$

How much to transfuse: the Goldilocks principle

Once a decision has been made to give red cells the next question is what volume should be transfused. Considering that each unit of blood represent a unique donor exposure it is crucial to give just enough and not too much, which may expose a child to multi donors or indeed be wasteful of such a valuable resource. Blood typically comes in two volumes - paediatric packs and adult units - approximately 50ml and 280ml respectively.

The quoted transfusion factor ranges from 3 to 5 but is poorly evidenced based. Davies et al. carried out a retrospective review of 564 transfusions on a paediatric intensive care unit over a 2 year period and proposed a transfusion factor equal to 3/haematocrit (Hct) level. Give that the UK standard Hct is 0.6 a factor of 5 was recommended. Thus a 10ml/kg transfusion typically gives a Hb increment of 20g/L.

Technical aspects of transfusion

It is recommended that red cell transfusions are kept out of temperature controlled storage for no more than 4 hours in order to reduce the risk of bacterial transmission. Practically this means that transfusions should be given within this time window but can be given more quickly if clinically indicated. Blood components must be transfused through a micron filter to remove micro-aggregates in order to prevent the accumulation of clots in the filter.

Normal maximum infusion rates for top-up transfusion is 5ml/kg/hr and so most centres opt to give blood over 3–4 hours. In the context of acute replacement for hypovolaemia blood can be given as a bolus however there is a theoretical risk of reperfusion injury with rapid infusion. It is thought that there is a degree of microvascular injury after transfusion but this has not been fully characterised.

Transfusions should be given in clinical areas where patients can be directly observed. Staff administering blood products must be trained to recognise and treat acute transfusion reactions (see adverse effects of transfusions below). Regular visual monitoring and observations must be carried out prior to and during transfusions in order to monitor for adverse reactions. It is recommended that minimum observations are carried out pre-transfusion, at 15 minutes into the transfusion and up to 60 minutes post-transfusion. Patients will typically need to be

Other potential adverse effects

Description

Hyperkalaemia	Due to high potassium content of supernatant of stored red cells and decreased cellular ATP production leading to leakage of potassium.
Storage lesions	Transfusion of red cells stored for more than 2 weeks due to reduced cell function and viability. Resulting in reduced oxygen delivery, electrolyte disturbance and effects on metabolic state particularly in the critically ill patient.
Cytokine release	Transfusion may activate white blood cells and cause release of pro-inflammatory cytokines leading to microcirculatory effects.
Thrombosis	Through cytokine mediated vasoconstriction, microcirculatory stasis, increased haematocrit and haemolysis of stored blood.
Air embolism	Risk with any intravenous infusion particularly when given rapid blood transfusion.

Table 3

observed up to 24 hours following blood transfusion for delayed reactions.

Adverse effects of transfusion

Infectious and antigenic transfusion reactions (see Tables 1–3) are now uncommon (1 in 7000 units transfused) but preventable deaths and significant morbidity still occurs. As mentioned above the Serious Hazards of Transfusion (SHOT) scheme has attributed most major incidents to human error. Clinicians must remain vigilant and aware of potential adverse reactions and act quickly to minimise complications and maintain transfusion safety.

Monitoring during transfusion is essential to monitor for symptoms of transfusion reactions. Intravenous chlorphenamine maleate (piriton) and hydrocortisone may be prescribed in case of a reaction. If a serious transfusion reaction is suspected – stop the transfusion; assess clinically and start resuscitation if necessary; check that the details on the patient's ID band and the compatibility label of the blood component match; call for medical assistance and contact the transfusion laboratory. It is recommended to report all serious adverse transfusion reactions, errors and near-miss incidents.

In most circumstances, stopping the transfusion will be the first line of treatment.

Conclusions

Red cell transfusion in paediatrics is common and may be life-saving but it is not without risk. UK national guidance provides detailed safety protocols and recommended measures to mitigate these risks. Clinicians should be aware of the rationale behind its use and an attempt to minimise the requirement for blood transfusion should be pursued. ◆

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Practice points

- Comprehensive safe transfusion guidance is provided in the UK through JPAC (www.transfusionguidelines.org), NHSBT (www.nhsbt.nhs.uk) and NICE (Blood Transfusion, 2015; ng24).
- Inappropriate transfusion in medical practice is common and may cause harm.
- Red cell transfusion is indicated in haemorrhage shock, anaemia and certain haematological diseases.
- In haemodynamically stable, acyanotic children a transfusion threshold of 70 g/l should be adopted.
- The majority of transfusion incidents are preventable and nearly always caused by human error.
- Adverse effects of blood transfusion are related to antigenic and infectious reactions.