Guidelines on transfusion for fetuses, neonates and older children

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The guideline is a revision of the 2004 British Committee for Standards in Haematology (BCSH) guideline on transfusion in neonates and older children (BCSH, 2004). Although there has been little evidence on which to base paediatric clinical transfusion decisions in the past, there have been a number of studies and national audits published over recent years that contribute to decision-making in this area. In addition there have been changes to other guidance, including the management of neonatal jaundice National Institute for Health and Clinical Excellence (NICE, 2010) and the requirement for cytomegalovirus (CMV) seronegative components.

The clinical section focuses largely on aspects relating to transfusion indications and administration, whereas the laboratory section contains most of the information relating to pre-transfusion testing and component selection. Details relating to blood component specification and typical transfusion volumes and rates may be found in Appendix 1.

Methods

The guideline writing group was selected to be representative of UK-based medical experts including specialists from fetal medicine, neonatology, paediatric intensive care, cardiac anaesthesia, paediatric haematology, clinical and laboratory transfusion medicine. The guideline is based on a systematic literature search subsequent to the 2004 guideline up to November 2014 together with other relevant papers identified. The search strategy is presented in Appendix 2. Information from other relevant international guidelines has also been considered. The writing group produced a draft guideline, which was subsequently revised by consensus following comment by members of the Transfusion Task Force of the BCSH and by a sounding board including UK haematologists, paediatricians/neonatologists. The 'GRADE' system was used to quote levels and grades of evidence (http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html). Recommendations entirely extrapolated from evidence from adult studies have been given a lower grade for children.

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of transfusion in fetuses, neonates and older children. The guidelines represent recommended UK practice. The guidance may not be appropriate for patients with certain rare disorders and does not cover unusual procedures, such as extracorporeal membrane oxygenation (ECMO). In all cases, individual patient circumstances may dictate an alternative approach.

Clinical transfusion

Introduction

Appropriate transfusion of fetal and paediatric patients of all ages is vital in order to balance transfusion benefits against risks. These risks include transfusion of an incorrect blood component due to errors, such as mistaken patient identity, or unpredictable acute transfusion reactions (Stainsby *et al*, 2008). Recent studies suggest that a significant percentage of paediatric transfusion recipients receive only one transfusion during their admission (Slonim *et al*, 2008; New *et al*, 2014), raising the possibility that some may be avoidable.

Specialized components are available for transfusion to different paediatric patient groups and for different clinical indications. Plasma components have been imported for all patients born on or after 1 January 1996 in order to reduce the risk of transfusion transmission of variant

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Creutzfeldt–Jakob disease (vCJD; see Section 7). Additional component safety measures are applied for fetal and neonatal patients, who are particularly vulnerable recipients because of their small size and developmental immaturity and who also have the longest potential lifespan. Information on components and their transfusion volumes is included in Section 7 and Appendix 1, with additional detail in the text where relevant.

Standard definitions of neonates (up to 28 d of postnatal age) and infants (>28 d to <1 year) are used. The definition of a child is <18 years, but in many cases children are admitted to adult wards from 16 years of age, and for these patients local blood transfusion administration transfusion policies for adults may be followed. Thresholds for transfusion are typically based on the haemoglobin concentration (Hb), platelet count and/or coagulation screen results (Venkatesh *et al*, 2013). These are surrogates for clinical transfusion need (and coagulation ranges in neonates are particularly difficult to interpret) but in most cases are the most pragmatic solution until there is evidence for better clinical measures.

The term 'clinically significant bleeding' has been used for some of the recommendations in the guideline. The most widely recognized approach to standardizing bleeding events in transfusion is the system is based on the World Health Organization (WHO) bleeding scale, which assigns different types and severities of bleeds to different grades between 1 and 4. Significant bleeding is typically considered at grades 2–4 (for example Stanworth *et al*, 2013; NICE, 2015). Although the WHO bleeding scale is more commonly used for clinical research in adults, we suggest that a pragmatic modification may be used to help guide transfusion decisions based on bleeding risk, taking into account the types of bleeding and changes in haemodynamic parameters appropriate for neonatal and paediatric patients in different clinical situations (see Section 4 for cardiac surgery).

1 Intrauterine transfusions

1.1 Principles

Intrauterine transfusions (IUTs) are invasive procedures with a risk of fetal death of 1–3% per procedure and up to 20% for hydropic fetuses, depending on the underlying aetiology of the anaemia (Lee & Kaufman, 2011). IUTs are only undertaken in specialized fetal medicine units with the requisite interventional skills and expertise. The National Clinical Reference Group has recommended that such centres are defined as those performing at least 15 procedures per year, with a minimum of two specialists. Although technically challenging, fetal blood sampling (FBS) and IUTs can be performed as early as 16 weeks gestation. IUTs can be performed as late as 34–35 weeks gestation, however the increased risk/benefit ratio must be considered with very late interventions. Complications of FBS/IUT include miscarriage/preterm labour, fetal bradycardia, cord haematoma, vessel spasm, bleeding from the puncture site and fetal death. The procedure is carried out under continuous ultrasound guidance with facilities for immediate analysis of the fetal blood Hb and haematocrit (Hct) or platelet count, allowing any decision to transfuse the fetus to be made concurrently.

Good multidisciplinary communication is essential between fetal medicine units undertaking the IUTs, the hospital transfusion laboratory and their counterparts in the hospital where the baby will be delivered.

1.2 Red cell IUT

Red cell IUTs are performed for the treatment of fetal anaemia, most commonly due to haemolytic disease of the fetus and newborn (HDN) caused by anti-D, -c or -K (Royal College of Obstetricians and Gynaecologists, 2014; BCSH, 2016a), or fetal parvovirus infection. Ultrasound monitoring using middle cerebral artery peak systolic velocities (MCA PSV) is generally done on a weekly basis for pregnancies at risk. MCA PSV monitoring is the standard technique for non-invasive diagnosis of fetal anaemia (Pretlove *et al*, 2009) and can predict moderate or severe fetal anaemia with 88% sensitivity and a false positive rate of 18% (Oepkes *et al*, 2006). If MCA monitoring suggests anaemia (MCA PSV >1·5 multiples of the median), FBS and possibly IUT are indicated. MCA PSV monitoring should be used with caution after 36 weeks as its sensitivity for the detection of fetal anaemia decreases. If there are concerns beyond this gestation because of raised MCA PSV, further advice should be sought from a fetal medicine specialist experienced in managing fetal anaemia.

IUT procedures may be required every 2–3 weeks, the frequency minimized by transfusing red cells of high Hct and the maximum volume. The aim of each transfusion is to raise the Hct to 0·45. In general, for red cell antibodies that could cause fetal anaemia but which have been stable throughout pregnancy and where the MCA PSV is normal, delivery should take place between 37 and 38 weeks of gestation. If an IUT has not been required but antibody levels are rising and there is evidence of fetal anaemia, then consideration of earlier delivery may be necessary. If an IUT has been required, the timing of delivery will depend on the degree of fetal anaemia, time from IUT, rate of fall in fetal Hb/Hct and gestation. It is important to ensure that antigen-negative blood is available at delivery for known pregnancies with HDN if it is anticipated that the baby will be anaemic.

After delivery, neonates with HDN following IUTs may become anaemic due to haemolysis or bone marrow suppression (Millard *et al*, 1990) and require monitoring for several weeks post-delivery (see 2.2.1). Anaemia persisting for a few weeks after birth is usually the result of passively acquired maternal antibodies causing continued haemolysis, in which case the baby will be jaundiced and the blood film will show

evidence of haemolysis. Late anaemia may develop due to a transient suppression of neonatal erythropoiesis by transfusion. Babies who have required several IUTs are at particular risk. All babies who have had an IUT require admission to a neonatal unit for early phototherapy and investigation for on-going haemolysis or anaemia.

1.2.1 Red cell transfusion and component type

- Red cells for IUT are irradiated to prevent transfusion-associated graft-versus-host disease (TA-GvHD) and have specific features (Appendix 1, Tables a and b). They have only a 24-h shelf life following irradiation and the supplying Blood Service ideally requires a minimum of 24 h notice. If an IUT is required urgently for an anaemic fetus then this should be discussed with medical staff from the Blood Services who can expedite preparation of a suitable pack or suggest a rapidly available alternative (see below). As with neonatal exchange transfusion, if maternal antibodies other than anti-D, -c, -C, -E or -K are present, additional notice is required, where possible, to ensure that suitable blood negative for all relevant antigens is available.
- Blood for IUT should not be transfused straight from 4°C storage due to risks of fetal bradycardia but there are no specifically designed warming systems for the small blood volume required and the component should not be exposed to radiant heaters or sunlight as the temperature is unmonitored and there is a risk of haemolysis.
- Transfusion volume required may be calculated based on donor and fetal Hcts and the estimated fetoplacental blood volume (Rodeck & Deans, 2008). The fetoplacental volume depends on gestation and fetal weight.
- In urgent situations, if IUT units are unavailable, acceptable alternatives are irradiated neonatal red cell exchange units or irradiated paedipacks (small-volume splits of single-donor units, Appendix 1, Table b). These are available at all times from the Blood Services, so use of non-irradiated blood for IUTs should be extremely rare. In emergency situations where requesting irradiated red cells from the Blood Services would cause life-threatening delay, it may be necessary to use a non-irradiated alternative, ideally a fresh neonatal paedipack (before the end of Day 5 following donation, see 7.1.5) or an exchange transfusion unit (see Appendix 3). The risk of TA-GvHD using these alternatives, although not eliminated, is acceptable in an emergency because these components have been leucodepleted and in most cases there will be no shared haplotype between donor and recipient. Maternal blood should not be used for IUTs because of the significant risk of TA-GvHD (Bolton-Maggs *et al*, 2013).

1.3 Platelet IUT

Intrauterine platelet transfusions are usually given to correct fetal thrombocytopenia caused by platelet alloimmunization: 'neonatal alloimmune thrombocytopenia' (NAIT). Alloantibodies to human platelet antigens (HPA)-1a, HPA-5b and HPA-3a account for almost all cases of NAIT, the commonest being anti-HPA-1a (80–90% of cases). In most cases fetal transfusion can be avoided by treating the mother with intravenous immunoglobulin (IVIg) and/or corticosteroids (Peterson *et al*, 2013). Compatible platelets should be available at the time of diagnostic fetal sampling for NAIT, in order to prevent fetal haemorrhage if severe thrombocytopenia is detected, the risk of which increases substantially with platelet counts $<50 \times 10^9$/l.

1.3.1 Platelet component and transfusion

- Platelets provided for IUT are HPA compatible with maternal antibody and irradiated
- The volume transfused is calculated based on the fetal and concentrate platelet count
- Platelets should be transfused more slowly than red cells for IUT because of increased risk of fetal circulatory stasis and stroke.

Key practice points

1 *Fetal blood counts should be rapidly available using near patient analysers and a blood film should subsequently be made to confirm the count and underlying diagnosis.*
2 *There must be good communication between the Blood Services, hospital transfusion laboratories and clinical staff to ensure timely provision of correct blood components for red cell and platelet IUTs. It is essential to communicate with the hospital where the baby is subsequently delivered so that appropriate (irradiated) components can be ordered.*

Recommendations

1 Red cells specific for intrauterine transfusion (IUT) should be used whenever possible. Fetal Medicine Units in conjunction with Hospital Transfusion teams should develop local written protocols and provide education regarding the hierarchy of possible alternatives for emergency IUT (Appendix 3) (1C).
2 Maternal blood should NOT be used for IUT due to the risk of transfusion-associated graft-versus-host disease (TA-GvHD) (1B).

2 Transfusions to neonates

2.1 Principles

Transfusion triggers for neonates will vary depending on the clinical context, including the gestational age at birth. Neonatal transfusion guidelines have generally been developed as a result of neonatal studies predominantly of very low birth weight (VLBW; <1·5 kg) babies. In neonatal

intensive care units (NICUs) most transfusions are given to preterm neonates (mostly <32 weeks gestational age; National Comparative Audit of Blood Transfusion, 2010), some of whom will require transfusion beyond 28 d of life. In general, babies of all gestational and postnatal ages on NICUs will tend to be transfused using the same guidelines although there is little evidence specifically related to term babies.

2.2 Red cell transfusions

The majority of extremely preterm neonates (<28 weeks gestation) receive at least one red cell transfusion as they frequently become anaemic, partly caused by phlebotomy losses (note: a 0·5 ml blood sample in a 500 g infant (1 ml/kg), is roughly equivalent to a 70 ml sample in a 70 kg adult), sometimes with sample volumes larger than required (Lin *et al*, 2000). Use of cord blood for initial blood tests for VLBW neonates has been advocated in order to reduce the need for transfusion (Baer *et al*, 2013), but results should be interpreted with caution if there are sampling difficulties. Neonatal transfusions are usually given as small-volume 'top-up' transfusions, to maintain the Hb above a particular threshold or because of the presence of surrogate markers of anaemia, such as poor growth, lethargy or increased episodes of apnoea.

Potential benefits of transfusion in this group include improved tissue oxygenation and a lower cardiac output to maintain the same level of oxygenation (Fredrickson *et al*, 2011). These benefits need to be weighed against possible adverse outcomes (Christensen & Ilstrup, 2013). In addition to the standard risks associated with transfusion, necrotizing enterocolitis (NEC) may follow neonatal transfusion, although a causal link has not been demonstrated (Christensen, 2011; Paul *et al*, 2011; Mohamed & Shah, 2012). The use of paedipacks reduces donor exposure for these multiply transfused preterm infants (Wood *et al*, 1995; Fernandes da Cunha *et al*, 2005; Strauss, 2010a). Although sequential use of paedipacks may result in the use of older blood, the Age of Red Blood Cells in Premature Infants (ARIPI) trial reported no effects on clinical outcomes for preterm neonates using red cells of different storage ages (Fergusson *et al*, 2012).

Key practice points

1 *Hospitals should develop policies that help to minimize exposure of infants to multiple donors (see 7.1.4).*
2 *Minimize phlebotomy where possible: agree a local policy on the frequency and types of regular blood tests required, collecting small samples, and using small-volume laboratory analysers and near-patient testing.*
3 *Hospital policies should ensure that paedipacks are available for emergency use by maternity and neonatal units (Appendix 1, Table b; see 7.2). The laboratory should be notified once they have been used.*

2.2.1 Exchange transfusion

Indications and aims

Exchange blood transfusion (EBT) is performed to manage a high or rapidly rising bilirubin not responsive to intensive phototherapy or IVIg (NICE, 2010), or for severe anaemia. EBT is mainly used in the treatment of HDN to prevent bilirubin encephalopathy by removing the antibody-coated red cells and excess bilirubin. It may also be required for neonatal hyperbilirubinaemia due to other causes, such glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Exchange blood transfusion is a specialist procedure with associated risks (Ip *et al*, 2004; Smits-Wintjens *et al*, 2008) and is now infrequently performed in most neonatal units mainly as a result of the reduction in HDN following routine antenatal anti-D prophylaxis for D-negative women (BCSH, 2014a) and the ready availability of intensive phototherapy. EBT must take place in an intensive care setting with intensive physiological and biochemical monitoring, carried out by staff trained in the procedure, following written informed parental consent (www.bapm.org/publications/documents/guidelines/procedures.pdf).

A single blood volume EBT will remove 75% of the neonatal red cells, and a double volume (160–200 ml/kg depending on gestational age) up to 85–90% red cells (Lathe, 1955; Sproul & Smith, 1964), and up to 50% of circulating bilirubin (Forfar *et al*, 1958). A double-volume exchange transfusion should be more successful in removing antibody-sensitized neonatal red cells and reduce the need for a subsequent EBT, but there is little direct evidence (Thayyil & Milligan, 2006).

Key practice point

Prior to and following discharge, babies who received EBT (and/or IUT) should have on-going close monitoring, both clinically and haematologically (with full blood count, reticulocytes, blood film and, if necessary, serum bilirubin), until the haemolysis resolves and the Hb starts to rise (see also 1.2). While these babies still have evidence of haemolysis they should receive folic acid supplementation.

Component and procedure specifications

- A specific red cell component for neonatal exchange transfusion is provided by the UK Blood Services, usually group O, and should also be compatible with any maternal antibody. Red cell units for neonatal exchange transfusion are rarely available immediately from the hospital transfusion laboratory and need to be requested with sufficient notice to allow for irradiation and transportation to the hospital. When HDN is caused by an unusual antibody, it may take longer for red cell units to be provided by the Blood Services, and at least 24 h notice should be given if possible. In emergency situations, it is occasionally necessary to use antigen-negative red cells in saline, adenine, glucose and mannitol

(SAGM) if red cells specific for exchange transfusion cannot be provided in time. The baby will require careful biochemical monitoring e.g. for possible rebound hypoglycaemia.
- Red cells suitable for neonatal exchange are irradiated and 'fresh' (before the end of Day 5 following donation, see 7.1.5), with a 24-h shelf-life post-irradiation in order to reduce the risk of recipient hyperkalaemia. They have a controlled Hct 0·5–0·6 (NHS Blood and Transplant [NHSBT] 0·5–0·55), in order to reduce the risk of both post-exchange anaemia and polycythaemia (see Appendix 1, Table b). They are negative for high-titre anti-A and anti-B antibodies (HT negative).
- EBT should not be undertaken with red cells straight from 4°C storage, and an approved/CE-marked blood-warming device can be used to avoid hypothermia (AABB 2012). However, use of a blood warmer is only appropriate if the infusion is given at a constant rate (warming is not suited to the intermittent bolus nature of a single vessel EBT where the 'push-pull' cycle method is used). Blood warming during EBT should not be uncontrolled, e.g. infusion lines exposed to a radiant heater (AABB, 2012), because of the risk of red cell haemolysis.

Recommendations

1 **Neonatal intensive care units (NICUs) should have local protocols for exchange blood transfusion (EBT) procedures. There should be early contact with the local hospital transfusion laboratory, which will contact the Blood Services to request specific red cells suitable for neonatal exchange transfusion (1C).**
2 **If an exchange blood transfusion is required, a double volume procedure should be undertaken (1C).**

Haemodilution for polycythaemia ('partial exchange transfusion')

Polycythaemia and hyperviscosity can occur in situations of chronic fetal hypoxia, e.g. growth restricted infants, and following twin-to-twin transfusion. Although neonatal hyperviscosity has been implicated as a cause of long-term neurodevelopmental delay (Delaney-Black *et al*, 1989; Drew *et al*, 1997), the use of haemodilution (described by neonatologists as 'partial exchange transfusion') for the treatment of polycythaemia is controversial. There is no evidence of long-term benefit and the procedure has been associated with up to an 11-fold increase in risk of NEC (Dempsey & Barrington, 2006; Özek *et al*, 2010), although the confidence intervals are wide. For the haemodilution procedure there is minimal difference in the effectiveness of plasma, 5% albumin or crystalloid in reducing haematocrit and no difference in viscosity or symptom relief (de Waal *et al*, 2006). Therefore to minimize risks associated with use of blood products, normal saline should be used if haemodilution is undertaken.

Recommendation

The use of haemodilution (partial exchange transfusion) for treatment of polycythaemia is not supported by evidence, and not recommended in the asymptomatic patient (1A). Its use in the symptomatic patient requires clinical judgement to assess the risks and benefits (2C).

2.2.2 Small volume transfusion

The majority of red cell transfusions to neonates are top-up transfusions of small volumes (traditionally 10–20 ml/kg, typically 15 ml/kg over 4 h) given to replace phlebotomy losses in the context of anaemia of prematurity, particularly for preterm VLBW neonates. There is very limited evidence to define optimal volumes for neonatal red cell transfusions, particularly relating to long-term outcomes. Volumes greater than 20 ml/kg may increase the risk of volume overload in non-bleeding patients. Therefore, in the context of data supporting restrictive transfusion thresholds from patients of all age groups including neonates, and the recommendations for older children (see 3.1), it seems prudent to use top-up transfusion volumes of 15 ml/kg for non-bleeding neonates in most cases.

There is evidence that having a blood transfusion policy and a method of ensuring its implementation has an impact in reducing the number of red cell transfusions (Baer *et al*, 2011). Hb levels are widely used as a marker of need for transfusion despite the limitations (Banerjee & Aladangady, 2014). Specific thresholds of Hb at which neonates are transfused vary according to the cardiorespiratory status and postnatal age of the infant, partly following the normal physiological reduction in Hb over the first few weeks of life (National Comparative Audit of Blood Transfusion, 2010; Whyte & Kirpalani, 2011).

Since publication of the previous BCSH guidelines (BCSH, 2004), three randomized studies addressing 'restrictive' *versus* 'liberal' transfusion thresholds for neonatal red cell transfusion in VLBW babies have been published (Iowa study, Bell *et al*, 2005; Premature Infants in Need of Transfusion (PINT), Kirpalani *et al*, 2006; Chen *et al*, 2009), and these are included in updated systematic reviews (Whyte & Kirpalani, 2011; Venkatesh *et al*, 2012). Liberal transfusion thresholds were those more typically applied in the past, by comparison to policies describing more restricted use of red cells (at lower 'restrictive' thresholds by Hb or Hct). The trials in neonates reported a small and variable reduction in the number of transfusions with restrictive regimens. For the restrictive group (transfused at lower Hbs), at short-term follow-up the Iowa study (Bell *et al*, 2005) reported an increase in episodes of apnoea, and at 18–21 month follow-up the PINT study found a statistically significant cognitive delay in a *post-hoc* analysis (Whyte *et al*, 2009). For the liberally transfused group, the Iowa study patients had significantly poorer learning outcomes (McCoy *et al*, 2011) and reduced brain volume on magnetic resonance imaging (Nopoulos

et al, 2011). However, information on long term outcomes is limited and contradictory and overall there is no evidence that restrictive transfusion policies have a significant impact on mortality or major morbidity (Whyte & Kirpalani, 2011). It should be noted that safety of Hb thresholds below those used in the trials is unknown.

Suggested red cell transfusion thresholds for very preterm neonates are given in Table I. They have been developed from the restrictive thresholds of the recent randomized controlled trials of VLBW babies (gestational ages mostly <31 weeks gestation) and are consistent with the neonatal transfusion data from the National Comparative Audit of Blood Transfusion (2010). The precise thresholds used will depend on the clinical situation. Further evidence based on short-term and long-term outcomes should become available from the multicentre randomized controlled trial (RCT) ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcome of extremely low birth weight infants; ETTNO Investigators, 2012), and the TOP-trial (Transfusion of Prematures trial; Clinicaltrials.gov NCT01702805).

There is no specific evidence relating to transfusion of infants with chronic lung disease (CLD; defined as oxygen dependency beyond 28 d of age). Ex-preterm infants with CLD should be transfused as suggested in Table I, taking into account their clinical status. Some clinicians may accept Hbs as low as 80 g/l with adequate reticulocytes. There is no justification for top-up transfusion simply because the baby is about to be discharged.

Table I does not include suggested thresholds for moderate to late preterm (≥32 weeks gestational age at birth) or term neonates, as there is little evidence regarding the appropriate thresholds for these groups. Clinicians may consider similar thresholds to those used for preterm babies off oxygen.

Erythropoietin (EPO)

There are several systematic reviews and over 30 trials of EPO use in neonates (Aher & Ohlsson, 2012, 2014; Ohlsson & Aher, 2014). EPO may reduce red cell transfusion requirements in neonates but its effect appears to be relatively modest whether given early or late. EPO has been suggested to have broader neuroprotection roles, but risks include the development of retinopathy of prematurity (ROP) related to pathological neovascularization (Aher & Ohlsson, 2014). Although underpowered for ROP, a recent RCT of EPO and darbepoeitin alfa (a novel erythropoiesis stimulating agent) in 102 preterm infants reported a significant reduction in transfusion requirements and donor exposures in both the EPO and darbepoeitin alfa groups compared with placebo (Ohls *et al*, 2013). EPO may be considered for preterm babies of parents who object to transfusion, e.g. Jehovah's Witnesses, but may not prevent the need for transfusion.

Table I. Suggested transfusion thresholds for preterm neonates.*

	Suggested transfusion threshold Hb (g/l)		
Postnatal age	Ventilated	On oxygen/ NIPPV‡	Off oxygen
First 24 h	<120	<120	<100
≤ week 1 (d 1–7)	<120	<100	<100
week 2 (d 8–14)	<100	<95	<75†
≥ week 3 (d 15 onwards)	<100	<85	<75†

*Standard definition of preterm is <37 weeks gestational age at birth but table applies to very preterm neonates (<32 weeks).
†It is accepted that clinicians may use up to 85 g/l depending on clinical situation.
‡NIPPV, non-invasive positive pressure ventilation.

Placental transfusion including delayed cord clamping

Delayed cord clamping (DCC) of at least 1 min is recommended for the term and preterm neonate not requiring resuscitation (Wyllie *et al*, 2015). Systematic reviews of DCC in term neonates have shown significantly increased Hb after birth and decreased iron deficiency at 2–6 months of age (Hutton & Hassan, 2007; McDonald *et al*, 2013). There was a significant increase in asymptomatic polycythaemia (Hct >65%) and a tendency to increased blood viscosity following DCC (Hutton & Hassan, 2007). In preterm neonates with DCC, the Hb is higher after birth, together with higher blood pressure and reduced red cell transfusion requirement (Rabe *et al*, 2012; Ghavam *et al*, 2014). However, although Rabe *et al* (2012) found reduction in intraventricular haemorrhage (IVH) (all grades together) the numbers were too small to comment on the clinically significant IVHs (grade 3 or 4), and there is paucity of evidence about the long-term neurodevelopmental outcomes. Further RCT evidence is needed for DCC in the very preterm neonate and those in need of resuscitation at birth, e.g. Australian Placental Transfusion Study (APTS); (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=335752).

Recommendations

1 **Studies to date support restrictive transfusion thresholds (2B) and suggested Hb thresholds for top-up transfusions are given in Table I.**
2 **Transfusion volumes of 15 ml/kg are generally recommended for non-bleeding neonates (2C).**
3 **The routine use of EPO or darbepoeitin alfa is not recommended in preterm infants to reduce transfusion (1B).**
4 **Where the term neonate (1B) or preterm neonate (2C) does not require resuscitation, undertake delayed cord clamping.**

2.2.3 Surgery and large volume neonatal transfusion (non-cardiac)

For surgery in neonates, the thresholds given in Table I may be used, as there is no evidence that higher perioperative Hbs are required (for neonates on cardiopulmonary bypass see Section 4). Large volume transfusion, defined as at least equivalent to a single circulating blood volume (approximately 80 ml/kg for neonates) over 24 h or 50% of the circulating volume within 3 h, may be needed for specific types of neonatal surgery, e.g. craniofacial or liver surgery. If major blood loss (>40 ml/kg) is anticipated, consideration should be given to the use of antifibrinolytic agents, such as tranexamic acid, although there is little published evidence in neonates undergoing non-cardiac surgery. Cell salvage for neonates with large volume blood loss is technically feasible and could be used to reduce allogeneic transfusion as in older children (Section 3.2.4). For situations of massive haemorrhage in neonates, it seems reasonable to apply the principles of the management of major bleeding in children (Section 5) although there is little evidence for this age group (Diab *et al*, 2013).

There is a risk of hyperkalaemia following large volume transfusions, particularly if infused rapidly (Strauss, 2010b; Vraets *et al*, 2011; Lee *et al*, 2014), so it is recommended that red cells for large volume neonatal and infant transfusions (Appendix 1, Table b) are used before the end of Day 5 following donation (and within 24 h of irradiation) in order to reduce this risk in the recipient (see Sections 4.1 and 7.1.5). Rapid transfusion via a central line may represent a particular risk, and the alternative use of large bore (greater than 23 g) peripheral lines in small babies may not always be technically feasible. Serum electrolyte concentrations should be monitored frequently, including calcium (to prevent hypocalcaemia secondary to citrate overload) and potassium. All large volume transfusions should be given via a blood warmer to avoid the development of hypothermia and the core temperature should be monitored, as recommended for adults (NICE, 2008).

Recommendation

Transfuse red cells for large volume neonatal and infant transfusion before the end of Day 5 following donation (1C).

2.3 Neonatal platelet transfusions

The use of platelet transfusions for neonates with thrombocytopenia and active bleeding is considered appropriate, but there is uncertainty and practice variation in the wider use of platelet transfusions for prophylaxis in the absence of bleeding. In an evidence-based review of the use of platelets, Lieberman *et al* (2014a) noted that most studies explored the relationships between thrombocytopenia and clinical outcomes rather than the direct effects of platelet transfusions. In a multicentre prospective observational study of 169 neonates with platelet counts of less than 60×10^9/l, most transfusions were prophylactic and given to pre-term neonates, and many were given after the period when major bleeding, including IVH, occurs most frequently. Most infants received platelet transfusions within a range of pre-transfusion platelet counts between 25 and 50×10^9/l (Stanworth *et al*, 2009). There has been only one RCT in neonates to assess a threshold level for the effectiveness of prophylactic platelet transfusions (to compare prophylactic platelet thresholds of 50 vs. 150×10^9/l) (Andrew *et al*, 1993), and the recruited patient population in that trial, conducted over 20 years ago, may be of limited relevance to current neonatal practice. A randomized trial of prophylactic platelet thresholds is on going in the UK, Ireland and the Netherlands (International Standard Randomized Controlled Trial Number [ISRCTN] 87736839; www.planet-2.com; Curley A. *et al*, 2014). Other studies are required to address gestational age- and postnatal age-specific effects on neonatal platelet function (Ferrer-Marin *et al*, 2013).

In the absence of results from RCTs in this patient group, recommendations for prophylactic platelet transfusion are made on the basis of clinical experience. Suggested thresholds for pre-term infants and those with NAIT are summarized in Table II. While these may also apply to term neonates (e.g. those admitted to paediatric intensive care units (PICUs)), many paediatricians might consider more liberal use of platelets in unstable preterm neonates and more restrictive use in stable term infants. In the absence of specific evidence on platelet thresholds for prophylaxis before invasive procedures, recommendations for older children may be followed (see Table III). Information on neonates undergoing cardiac surgery is described later (Section 4.4).

Neonatal alloimmune thrombocytopenia (NAIT)

NAIT results most commonly from maternally derived anti-HPA-1a or 5b platelet antibodies. All neonates with NAIT (or

Table II. Suggested thresholds of platelet count for neonatal platelet transfusion.

Platelet count ($\times 10^9$/l)	Indication for platelet transfusion
<25	Neonates with no bleeding (including neonates with NAIT if no bleeding and no family history of ICH)
<50	Neonates with bleeding, current coagulopathy, before surgery, or infants with NAIT if previously affected sibling with ICH
<100	Neonates with major bleeding or requiring major surgery (e.g. neurosurgery)

NAIT, neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage.

suspected NAIT) and thrombocytopenia after birth should be discussed with a haematologist. Severely thrombocytopenic neonates with suspected NAIT should receive platelet transfusions at thresholds depending on bleeding symptoms or family history (see Table II). The suggested threshold of 25×10^9/l in the absence of bleeding is the same as that for neonates without NAIT, but it is acknowledged that this is not evidence-based. Results of diagnostic serological tests may not be available immediately, but the UK Blood Services stock platelets that are negative for HPA-1a/5b antigens, antibodies to which are responsible for over 90% of cases. A post-transfusion platelet count should be measured to check the increment. The baby should be monitored for intracranial haemorrhage (ICH) by cranial ultrasound and, if there is evidence of ICH, platelet transfusions should be given to maintain platelet counts between 50 and 100×10^9/l for the period that the baby is felt to be at highest risk of on going haemorrhage.

If HPA-1a/5b-negative platelets are unavailable or ineffective in producing a platelet rise (Department of Health, 2008), random donor platelets and/or IVIg may be used, which may reduce the need for platelet transfusions until spontaneous recovery in platelet count occurs 1–6 weeks after birth (see also Section 7.2).

Recommendations

1 **For preterm neonates with very severe thrombocytopenia (platelet count below 25×10^9/l) platelet transfusions should be administered in addition to treating the underlying cause of the thrombocytopenia (Grade 2C). Suggested threshold counts for platelet transfusions in different situations are given in Table II (2C).**
2 **Consider intravenous immunglobulin in NAIT refractory to platelets negative for HPA-1a/5b antigens or if antigen-matched platelets are unavailable (1C).**

2.4 Neonatal fresh frozen plasma (FFP) and cryoprecipitate

2.4.1 FFP

There is considerable uncertainty about appropriate use of FFP in neonates, which reflects the lack of evidence in this area. National audits have shown high proportions of FFP transfusions are given for prophylaxis: 42% of infant FFP transfusions in a UK audit (Stanworth *et al*, 2011) and 63% in a similar Italian audit (Motta *et al*, 2014). Prophylactic use of FFP, including prior to surgery, is of unproven benefit and uncertainty is compounded by the difficulty in defining a significant coagulopathy in this age group. A large RCT reported by the Northern Neonatal Nursing Initiative (NNNI Trial Group, 1996) reported no benefit from prophylactic FFP given to neonates to prevent ICH, although the study did not assess coagulopathy and the gestational age distribution of enrolled babies would not reflect current neonatal practice. More recent non-randomized studies in preterm infants (Dani *et al*, 2009; Tran *et al*, 2012) have shown inconsistent benefits from coagulopathy screening and early plasma use for prevention of IVH.

Neonates have a different balance of procoagulant and anticoagulant proteins compared to older children, although overall haemostasis may be functionally adequate when defined by global measures of haemostasis (Tripodi *et al*, 2008). This results in different postnatal and gestational age-related coagulation ranges in the first months of life, particularly for the activated partial thromboplastin time (APTT) (Andrew *et al*, 1987, 1988; Monagle *et al*, 2006). Most laboratories rely on previously published neonatal ranges due to difficulties in obtaining locally-derived ranges in this age group but variation in reagents and analysers can make interpretation of results difficult, and the widely quoted work is now dated. Polycythaemia with a raised Hct may further contribute to apparent prolongation of coagulation times, in particular the prothrombin time (PT). In older children and adults, coagulopathy is often defined as a PT or APTT greater than 1·5 times the mid-point of normal range, but this is more difficult to apply in neonates, especially in very preterm neonates, given that the ranges may be uncertain and broad. Moreover disseminated intravascular coagulation (DIC) is a poorly defined entity in neonates.

Routine coagulation screening of babies admitted to NICUs may lead to increased transfusion and it is unclear, from retrospective studies, whether mild/moderate abnormalities are predictive of bleeding (Catford *et al*, 2014; Christensen *et al*, 2014). Coagulation screening should therefore only be undertaken for selected neonates with evidence of bleeding or at high risk of DIC, such as those with NEC or severe sepsis. Although most neonatal coagulopathies will be secondary to acquired bleeding disorders, undiagnosed congenital bleeding disorders should also be considered (see Section 3.4.8). For transfusion management of DIC see Section 3.4.3.

Key practice points

1 *A policy of routine coagulation screening is inappropriate as results are difficult to interpret in neonates and routine testing may lead to increased transfusion of FFP without benefit.*
2 *Wherever possible, a sample for testing should be taken prior to transfusion. Although correction of abnormal coagulation screens by FFP is unpredictable it is good practice to recheck tests following transfusion.*

Recommendations

1 **There is no evidence to support the routine use of fresh frozen plasma (FFP) to try to correct abnormalities of the coagulation screen alone in non-bleeding neonates (1C).**
2 **FFP may be of benefit in neonates with clinically significant bleeding (including massive blood loss) or prior to invasive procedures with a risk of significant bleeding, and who have an abnormal coagulation profile, defined**

as a PT or APTT significantly above the normal gestational and postnatal age-related reference range (taking into account local reference ranges where available) (2C).

3 **FFP should not be used for simple volume replacement or routinely for prevention of IVH (1B).**

2.4.2 Purpura fulminans secondary to severe homozygous deficiency of protein C or protein S

Neonatal purpura fulminans (PF) may be the presenting feature of a severe deficiency of either protein C (PC) or, less commonly, protein S (PS) (Chalmers *et al*, 2011; Price *et al*, 2011). These deficiencies are due to pathological mutations in the *PROC* and *PROS1* genes respectively. Neonatal PF is a haematological emergency characterized by skin necrosis and DIC that may progress rapidly to multi-organ failure. Early recognition is crucial to reduce morbidity and mortality. While PC concentrate has better efficacy in the management of PC deficiency, early empiric FFP (15–20 ml/kg given 8–12 hourly) is likely to be required until the diagnosis is confirmed and PC concentrate is made available (Dreyfus *et al*, 1995). FFP is the only available treatment for severe PS deficiency (Mahasandana *et al*, 1996).

Recommendations

1 **FFP is appropriate for the early management of severe hereditary protein C deficiency but should not be used in preference to protein C concentrate if this is available (2B).**

2 **FFP should be used for the management of severe hereditary protein S deficiency (2C).**

2.4.3 Neonatal cryoprecipitate

Overall, the management of low fibrinogen is the same in neonates as in children. Severe congenital hypofibrinogenaemia (see Section 3.4.8) may present in the neonatal period but neonatal hypofibrinogenaemia is most likely to be acquired, secondary to DIC (see Section 3.4.3) or liver dysfunction (see Section 3.4.4). Cryoprecipitate may also be indicated in neonatal cardiac surgery and major haemorrhage (see Sections 4 and 5).

2.4.4 Vitamin K deficiency bleeding

Vitamin K deficiency bleeding (VKDB) may occur and require urgent treatment if major bleeding occurs in neonates or children. Four factor prothrombin complex concentrate (PCC) is preferable to FFP, although there is little published data on this indication. Vitamin K is recommended for every newborn infant, and bleeding may occur after missed prophylaxis (Clarke & Shearer, 2007).

2.5 Neonatal granulocyte transfusions

A recent Cochrane review identified 4 RCTs which addressed the effect of granulocyte or buffy coat transfusions as adjuncts to antibiotics after confirmed or suspected sepsis in neutropenic neonates (Pammi & Brocklehurst, 2011). The authors concluded that the evidence from RCTs was insufficient to support or refute the routine use of granulocyte transfusions in septic neutropenic neonates.

Recommendation

There is insufficient evidence to recommend the routine use of granulocyte transfusions for neonates (Grade 2C).

2.6 T-activation

T-activation occurs when sialic acid residues are stripped from the red cell surface by neuraminidase producing organisms, exposing the T-cryptantigen. It can occur in infants with NEC and children with *S. pneumoniae* infection, including pneumococcus-associated haemolytic uraemic syndrome (pHUS) (Crookston *et al*, 2000). T-activation can be detected using a lectin panel. Anti-T antibodies are naturally occurring IgM antibodies in adult plasma, developing during infancy and absent in neonates. A causal role for anti-T antibodies in post-transfusion haemolysis of T-activated red cells or in the pathogenesis of pHUS has not been established (Crookston *et al*, 2000; Eder & Manno, 2001; Ramasethu & Luban, 2001; Johnson & Waters, 2012). Investigation for T-activation in infants with NEC in whom haemolysis has occurred following transfusion and in children with suspected pHUS should include a lectin test for T-activation (for further information see Massey, 2011).

If transfusion is required for neonates with T-activation (usually in the context of NEC) and haemolysis following previous transfusion, red cells in SAGM are suitable as these contain little plasma. If platelets or FFP are clinically indicated (see Sections 2.3 and 2.4.1), 'washed' platelets in platelet suspension medium, or low-titre anti-T FFP (Appendix 1, Table d) may be used. There is no consensus as to the need for routine provision of these platelet and FFP components for children with pHUS (who are usually old enough to have developed anti-T) or for neonates with T-activation but no transfusion-related haemolysis.

Key practice point

The provision of special blood products for neonates with suspected T-activation and transfusion-related haemolysis requires close liaison between neonatologists and haematologists, including with the Blood Services. The time taken to provide special rather than standard components should be balanced against the urgency of transfusion. The causes of haemolysis should be investigated and other measures to treat

coagulopathy, such as use of vitamin K, employed where appropriate.

3 Transfusions to infants and children

This section relates to infants and children, excluding neonates.

3.1 Principles of red cell transfusion

The National Comparative Audit of Blood Transfusion of paediatric red cell transfusions reported that more than half of paediatric transfusions on non-neonatal wards were given to haematology/oncology patients (New *et al*, 2014). Other frequently transfused groups include those on PICU or undergoing cardiac surgery or ECMO. A significant proportion of children are transfused on general rather than specialist paediatric wards. Transfused children often have only a single transfusion during their admission (Slonim *et al*, 2008; New *et al*, 2014), and indications for transfusions should be followed carefully to ensure that they are not given unnecessarily. RCTs of different red cell transfusion policies have mostly been conducted in adults and systematic reviews indicate that liberal transfusion thresholds are not associated with benefit and may be associated with harm (Carson *et al*, 2012; Hébert & Carson, 2014; Rohde *et al*, 2014).

Most recent research has related to transfusion thresholds rather than optimal volumes for transfusion. Nonetheless, in the context of the evidence favouring restrictive thresholds, transfusions of single red cell units have been recommended for non-bleeding adults (BCSH, 2012a; NICE, 2015). In the absence of evidence to the contrary, this guideline recommends that the volume of red cells transfused should also be minimized for infants and children, taking into account the likelihood of requiring subsequent transfusions.

All children starting regular transfusions should be vaccinated against hepatitis B as early as possible (Sickle Cell Society, 2008). Those on chronic transfusion regimens should have an extended red cell phenotype/genotype (Section 8.4), particularly those with haemoglobinopathies, but also those with congenital dyserythropoietic anaemia, aplastic anaemia and other bone marrow failure syndromes. This should be performed prior to, or as soon as possible after, commencing regular transfusions. For chronically transfused paediatric patients, monitoring growth and development are important outcome measures of efficacy.

Key practice point

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 (see Section 6.1.2 for calculation), usually a maximum of one unit. Where arterial or central venous access is available (e.g. in theatres) use regular Hb estimation to ensure the smallest necessary volume is transfused.

3.2 Red cell transfusion

3.2.1 Paediatric intensive care

Transfusion indications in children are largely extrapolated from adult studies. However, the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study of red cell transfusions in stable critically ill children on PICU (Lacroix *et al*, 2007) compared a restrictive Hb transfusion threshold (70 g/l) vs. a liberal (95 g/l). The more restrictive transfusion practice (mean Hb 87 g/l vs. 108 g/l in the liberal group) was associated with reduced blood use and no significant increase in adverse outcomes. The findings were similar by subgroup analysis of patients including those with sepsis, non-cardiac surgery, and respiratory dysfunction (Lacroix *et al*, 2012). A transfusion threshold of 70 g/l in stable, non-cyanotic, patients on PICU is therefore considered reasonable based on current evidence in children. This threshold also concurs with the recommended threshold for most adult red cell transfusions following systematic reviews and an increasing evidence base (Carson *et al*, 2012; BCSH, 2013a; Hébert & Carson, 2014; NICE, 2015). For cyanotic patients see Section 4.

As on NICU, phlebotomy losses on PICU may contribute to anaemia, are associated with increased transfusion requirements (Fowler & Berenson, 2003; Bateman *et al*, 2008) and may be partially avoidable (Valentine & Bateman, 2012).

Key practice point

In order to reduce the requirement for red cell transfusions in paediatric intensive care, minimize blood sampling and use near patient testing where possible as for neonates.

Recommendation

Use an Hb threshold of 70 g/l pre-transfusion in stable non-cyanotic patients (1B). If the child is unstable or has symptomatic anaemia a higher threshold may be considered (2C).

3.2.2 Stem cell transplant/oncology

For paediatric haemopoietic stem cell transplant (HSCT) and oncology patients, there is no specific evidence to guide the optimum Hb transfusion threshold although current practice would suggest that a threshold between 70–80 g/l may be reasonable. In the acute setting, the TRIPICU study supports a threshold of 70 g/l. This threshold has been reported (Lightdale *et al*, 2012; Bercovitz & Quinones, 2013), and is also implied by the median pre-transfusion Hb of 74 g/l for oncology patients in the UK National Comparative Audit of Blood Transfusion (New *et al*, 2014) and of 72 g/l at a Canadian oncology centre (Lieberman *et al*, 2014b). A Canadian multicentre RCT in paediatric HSCT randomized between Hb triggers of 120 g/l and 70 g/l but was

closed after enrolling only six patients: those in the higher Hb arm developed veno-occlusive disease but those in the lower Hb arm did not (Robitaille *et al*, 2013). The authors recommend a threshold of 70 g/l as the standard of care. The results of a restrictive *versus* liberal transfusion RCT in adults undergoing HSCT are awaited (Tay *et al*, 2011).

For children undergoing HSCT for thalassaemia, some centres use hypertransfusion (for example keeping the Hb >130 g/l) during the peri-transplant period to try to reduce the incidence of donor chimerism (Amrolia *et al*, 2001), with the rationale that bone marrow hyperplasia may be associated with a decreased chance of successful transplant (Shen *et al*, 2008). However, there is insufficient evidence to make a specific recommendation.

There is little evidence to guide best practice for red cell transfusion in the setting of chronic anaemia other than in haemoglobinopathy patients (BCSH, 2016b,c; Yardumian et al, 2016). A threshold of 70 g/l may be insufficient in the long-term to support normal growth and development in non-haemoglobinopathy children with chronic anaemia. Practice is consensus-based, and for patients with Diamond–Blackfan anaemia, transfusion to keep the Hb above 80 g/l has been recommended (Vlachos *et al*, 2008). The management of iron overload and chelation is beyond the scope of this guideline.

Recommendations

1 **There is insufficient evidence to make recommendations for pre-transfusion Hb thresholds in paediatric haematology/oncology patients and those undergoing stem cell transplantation (2C).**
2 **Patients with chronic anaemia due to red cell aplasia may require an Hb threshold of 80 g/l (2C).**

3.2.3 Haemoglobinopathies

For children with sickle cell disease (SCD) or thalassaemia, the new BCSH SCD transfusion guidelines and the UK Thalassaemia Society clinical standards bring together guidance for both adults and children and should be referred to for these groups of patients (BCSH, 2016b,c; Yardumian *et al*, 2016; see also Section 8.4 and Appendix 1, Table b).

3.2.4 Surgery (non-cardiac)

Major blood loss in paediatric surgery mostly occurs in craniofacial, scoliosis and cardiac surgery (see Section 4, and also Section 2.2.3 for infant large volume transfusion). Prior to elective surgery, the preoperative Hb should be optimised by treating iron deficiency anaemia, which is common in children (Brotanek *et al*, 2008). With the exception of children with sickle cell disease (Howard *et al*, 2013), there is no evidence to suggest that children undergoing elective non-cardiac surgery require a higher Hb transfusion threshold than those on PICU (70 g/l; for cyanotic children see Section 4.1). Evidence from a subgroup analysis of 124 paediatric general surgery patients in the TRIPICU study (Rouette *et al*, 2010) supported a threshold of 70 g/l for stable postoperative patients, and this threshold has been also reported in paediatric scoliosis surgery (van Popta *et al*, 2014).

There is evidence that antifibrinolytics, such as tranexamic acid, reduce blood loss (Neilipovitz *et al*, 2001; Sethna *et al*, 2005; Tzortzopoulou *et al*, 2008; Verma *et al*, 2014), the amount of blood transfused (Song *et al*, 2013), or both (Goobie *et al*, 2011) in children undergoing craniosynostosis and scoliosis surgery. This is broadly consistent with evidence from adult surgery (Henry *et al*, 2011; Ker *et al*, 2013). However the appropriate dose is unclear (Royal College of Paediatrics and Child Health, 2012; Goobie, 2013), as is the incidence of serious side effects. Large well-designed RCTs are required to address these issues.

Cell salvage can significantly reduce allogeneic blood transfusion in adults (Carless *et al*, 2010) and with the development of small bowls, is feasible in infants as well as older children (Seyfried *et al*, 2014). Contraindications include sickle cell disease and other conditions characterized by red cell fragility. A careful risk assessment is essential in malignancy and abdominal injury when the salvaged blood may contain a high concentration of malignant cells or bacteria (Association of Anaesthetists of Great Britain and Ireland [AAGBI] Safety Guideline, 2009).

Key practice point

Cell salvage should be supported by a programme of staff training, accreditation and audit in order to ensure a product of a consistently high quality (*AAGBI Safety Guideline 2009*).

Recommendations

1 **The preoperative Hb should be optimised by treating iron deficiency anaemia (1C).**
2 **A perioperative Hb transfusion threshold of 70 g/l should be used in stable patients without major co-morbidity or bleeding (1C).**
3 **Tranexamic acid should be considered in all children undergoing surgery where there is risk of significant bleeding (1B).**
4 **Red cell salvage should be considered in all children at risk of significant bleeding undergoing surgery and where transfusion may be required, providing there are appropriately trained staff (2C).**

3.3 Platelet transfusion

Most platelet transfusions are given to critically ill children in PICU, haemato-oncology patients and those undergoing cardiac surgery. Children may also bleed during recovery

from HSCT and frequently receive prophylactic platelet transfusions. A recent systematic review summarized the effect of platelet transfusions on platelet count increment, bleeding and mortality and aimed to formulate recommendations for the use of platelet transfusions for non-bleeding critically ill children with severe thrombocytopenia (platelet count $<50 \times 10^9$/l; Lieberman *et al*, 2014a). Only one study relevant to critically ill children was identified (prospective cohort, $n = 138$) which reported no difference in mortality between transfused and non-transfused children in adjusted analyses (Agrawal *et al*, 2008).

There are very few descriptive data on patterns of bleeding and use of platelet transfusions in children with haematological malignancies. In a (*post-hoc*) subgroup analysis of a RCT of different platelet doses in patients with haematological malignancies (PLADO), higher rates of bleeding were noted in children, although the reasons for this difference compared to adults was not clear (Josephson *et al*, 2012). The optimal safe platelet count for routine lumbar punctures (LPs) for children on treatment for leukaemia is also uncertain. One of the few (and largest) case series to report on outcomes of children treated for acute lymphoblastic leukaemia undergoing LP reported no haemorrhagic complications in 941 procedures performed in children with platelet counts $<50 \times 10^9$/l who had not received a prophylactic platelet transfusion (Howard *et al*, 2000; Astwood & Vora, 2011). A recent survey of UK paediatric oncology centres showed that prior to LP, there was variation in accepted platelet transfusion threshold between 10 and 70–80 $\times 10^9$/l (E. Chalmers unpublished observation). For insertion of central venous catheters in patients with thrombocytopenia, a retrospective study in adults with acute leukaemia by Zeidler *et al* (2011) showed an increased risk of non-severe bleeding only in patients with platelet counts $<20 \times 10^9$/l.

Overall, there is insufficient evidence in children to significantly change recommendations made in the previous BCSH guidelines (BCSH, 2004). Suggested thresholds are shown in Table III. The precise platelet threshold used for individual patients or patient groups will depend on the presence of other clinical risk factors. Indications for platelet transfusion in children are consensus-based; in general, a platelet count of 10×10^9/l can be used as a transfusion trigger in non-infected well children, but higher thresholds are used for children who are unstable and/or bleeding. Patients with aplastic anaemia may be best managed without routine prophylactic platelet transfusions in order to reduce the risk of alloimmunization, apart from situations of increased risk of bleeding.

Platelet transfusions are not given on the basis of a low count alone in immune thrombocytopenias, such as immune thrombocytopenia (ITP), or in the thrombotic disorders heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (TTP/HUS). Platelets should only be used where there is life-threatening bleeding in HIT and TTP/HUS as there is a risk of exacerbating thrombosis (BCSH, 2012b,c; George & Al-Nouri, 2012; Balestracci *et al*, 2013; Goel *et al*, 2015).

Recommendations

1 **Given a lack of studies in paediatrics, recommendations for platelet transfusions in critically ill children or those with haematological/oncological malignancies who develop severe thrombocytopenia are drawn from the wider adult literature and recommendations (2C) (BCSH, 2016d; see Table III for suggested thresholds).**
2 **As pragmatic guidance, it is suggested that for most stable children prophylactic platelet transfusions should be administered when the platelet count is below 10×10^9/l, excluding patients with immune**

Table III. Suggested thresholds of platelet counts for platelet transfusion in children.

Platelet count ($\times 10^9$/l)	Clinical situation to trigger platelet transfusion
<10	Irrespective of signs of haemorrhage (excluding ITP, TTP/HUS, HIT)
<20	Severe mucositis
	Sepsis
	Laboratory evidence of DIC in the absence of bleeding*
	Anticoagulant therapy
	Risk of bleeding due to a local tumour infiltration
	Insertion of a non-tunnelled central venous line
<40	Prior to lumbar puncture†
<50	Moderate haemorrhage (e.g. gastrointestinal bleeding) including bleeding in association with DIC
	Surgery, unless minor (except at critical sites)
	• including tunnelled central venous line insertion
<75–100	Major haemorrhage or significant post-operative bleeding (e.g. post cardiac surgery)
	Surgery at critical sites: central nervous system including eyes

ALL, acute lymphoblastic leukaemia; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; HUS, haemolytic uraemic syndrome; ITP, immune thrombocytopenia; LP, lumbar puncture; TTP, thrombotic thrombocytopenic purpura.

**Note*: routine screening by standard coagulation tests not advocated without clinical indication; for laboratory evidence of DIC see Section 3.4.3.

†It is accepted that prior to lumbar puncture some clinicians will transfuse platelets at higher counts (e.g. 50×10^9/l) in clinically unstable children, non ALL patients, or for the first LP in newly-diagnosed ALL patients to avoid haemorrhage and cerebrospinal fluid contamination with blasts, or at lower counts ($\leq 20 \times 10^9$/l) in stable patients with ALL, depending on the clinical situation. These practices emphasise the importance of considering the clinical setting and patient factors.

thrombocytopenia, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome and heparin-induced thrombocytopenia who should only be transfused with platelets for life-threatening bleeding (2B).

3.4 FFP and cryoprecipitate

3.4.1 Principles

Fresh frozen plasma and cryoprecipitate may be administered either therapeutically for the management of bleeding or prophylactically. There is very little evidence of benefit from FFP administration in many settings where it is currently used (Stanworth *et al*, 2004; Yang *et al*, 2012) and significant variation in practice is seen. As a result it appears there is frequent inappropriate use of FFP (Stanworth *et al*, 2011). Although there is little direct evidence in children relating to the appropriate FFP transfusion volume, for example in patients with significant bleeding, higher doses are likely to have a greater effect on reducing the abnormality of coagulation tests.

In the UK, the main source of concentrated fibrinogen is cryoprecipitate, although FFP also contains fibrinogen. Fibrinogen concentrate is only licensed in the UK for treatment of congenital deficiency although it is sometimes used for acquired deficiency on an individual patient basis. There is no evidence of a benefit from prophylactic use of cryoprecipitate. The major indications for cryoprecipitate transfusion in infants and children are DIC with bleeding, bleeding following cardiac surgery and major haemorrhage. There remains controversy over the fibrinogen transfusion threshold for cryoprecipitate transfusion. There is no evidence to alter the previously recommended fibrinogen threshold of 1·0 g/l outside the setting of major bleeding. Fibrinogen threshold levels of 1·0 g/l are recommended for inherited hypofibrinogenaemia (BCSH, 2014b) but where there is rapid consumption e.g. in DIC or major haemorrhage, higher target thresholds for therapy may be recommended (Sections 3.4.3, 4.4 and 5).

There is increasing interest in point-of-care testing results, such as thromboelastography/thromboelastometry, but there is limited evidence as to how/whether these should guide transfusion in children in the absence of bleeding (see also Section 4.4.1).

Key practice points

1 *Transfuse FFP volumes of 15–20 ml/kg, using the higher volumes particularly in bleeding patients, and ensure monitoring of clinical outcome. However, care should be taken to avoid volume overload, particularly in vulnerable patients.*
2 *Transfuse cryoprecipitate volumes of 5–10 ml/kg, using the higher volumes particularly in bleeding patients, and ensure monitoring of clinical outcome and fibrinogen levels.*

3.4.2 Correction of minor acquired coagulation abnormalities in non-bleeding patients (excluding DIC)

One of the commonest reasons for the administration of FFP in both children and adults is for the correction of minor/moderate abnormalities of the PT/International Normalized Ratio (INR) in non-bleeding patients (Stanworth *et al*, 2011), often done prior to surgery or other invasive procedures. There is accumulating evidence that this approach is incorrect and that much of this FFP use is likely to be inappropriate and exposes patients to unnecessary risk. Minor abnormalities of the PT or INR are poorly predictive of surgical bleeding (Segal & Dzik, 2005; BCSH, 2008) and the effect of FFP in normalizing the PT/INR is poor. Two studies in adults and children assessing the effect of FFP in patients with INRs 1·1–1·6 and 1·1–1·85 found that FFP failed to significantly improve the INR in the majority of cases and also noted no relationship with bleeding (Abdel-Wahab *et al*, 2006; Holland & Brooks, 2006). Abnormalities of the PT or APTT should however be appropriately investigated.

Cryoprecipitate similarly should not be given to correct mild degrees of hypofibrinogenaemia in non-bleeding patients.

Recommendations

1 **Prophylactic FFP should not be administered to non-bleeding children with minor prolongation of the prothrombin time (PT) (2B)/activated partial thromboplastin time (APTT) including prior to surgery, although it may be considered for surgery to critical sites (2C).**
2 **Prophylactic cryoprecipitate should not be routinely administered to non-bleeding children with decreased fibrinogen including prior to surgery. It may be considered for fibrinogen <1 g/l for surgery at risk of significant bleeding or to critical sites (2C).**

3.4.3 Disseminated intravascular coagulation

Data on blood product support in children with DIC are limited and there are no guidelines for paediatric practice. Recommendations are therefore largely extrapolated from adult practice. The primary aim should be reversal of the underlying cause. Recent guidance published by the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis harmonizes guidelines published from the UK, Italy and Japan (Wada *et al*, 2013). These guidelines state that FFP may be useful in patients who are actively bleeding and who have either a prolonged PT/APTT (>1·5 times midpoint of normal range) or a decreased fibrinogen (<1·5 g/l) and that FFP should also be considered in patients with similar laboratory abnormalities prior to invasive procedures. The evidence for these recommendations is of low quality. Similar recommendations can be applied to children with

DIC. For children, evidence for a fibrinogen level of 1·0 vs. 1·5 g/l as a threshold for transfusion remains unclear. In practice, it is necessary to take into account clinical factors including the rate of fall of fibrinogen and severity of bleeding. FFP contains all the coagulation factors and fibrinogen, so is used in the first instance for DIC with bleeding, reserving cryoprecipitate for persistent hypofibrinogenaemia despite FFP. However, consideration may be given to giving cryoprecipitate as the initial treatment prior to FFP when the fibrinogen is very low (e.g. 0·5 g/l), dropping rapidly, or if there is major haemorrhage.

Fresh frozen plasma and cryoprecipitate should not be administered on the basis of laboratory tests alone but should be restricted to those with signs of bleeding or where invasive procedures are planned. A possible exception in clinical practice is children presenting with acute promyelocytic leukaemia, who may be at particularly high risk of developing bleeding problems and may require more aggressive initial support as part of their leukaemia management protocol (Breen *et al*, 2012). Patients should also be treated with vitamin K if deficiency is suspected.

Purpura fulminans (PF)

Purpura fulminans in children may occur in both inherited (see Section 2.4.2) and acquired deficiencies of protein C and S (Chalmers *et al*, 2011; Price *et al*, 2011) and requires urgent investigation to determine the most likely cause. Where inherited PC or PS deficiency is suspected (sometimes in combination with sepsis), initial treatment is usually with FFP as for neonates. Protein C concentrate is the treatment of choice for on-going management of severe homozygous protein C deficiency (see Section 2.4.2). In acquired PF, management of the underlying cause is crucial. There is much less evidence to support the use of PC and PS supplementation in PF due to sepsis although FFP is frequently used for this indication. PC concentrate has been reported to be of benefit in some studies (Veldman *et al*, 2010), but is not currently licensed for this indication.

Key practice points

1 *Make sure that patients are vitamin K replete; this may mean giving it routinely to sick children.*
2 *FFP (15–20 ml/kg given 8–12 hourly) may be used as first line therapy to treat acquired PF in association with PC or PS deficiency while the underlying cause is being investigated. The underlying cause should be treated, and it may be helpful to monitor PC/PS levels.*

Recommendation

FFP may be beneficial in children with DIC who have a significant coagulopathy (PT/APTT >1·5 times midpoint of normal range or fibrinogen <1·0 g/l) associated with clinically significant bleeding or prior to invasive procedures (2C). Cryoprecipitate may be given if the fibrinogen is <1·0g/l despite FFP, or in conjunction with FFP for very low or rapidly falling fibrinogen (2C).

3.4.4 Liver disease

Liver disease may be associated with a variable degree of coagulopathy. Severe liver failure is usually accompanied by profound coagulation derangement, including hypofibrinogenaemia. Lesser degrees of liver dysfunction may also be associated with abnormal coagulation but recent evidence shows that the haemostatic system is reset, with an accompanying reduction in the natural anticoagulants associated with an increased risk of thrombosis (Weeder *et al*, 2014). No RCTs have addressed the use of FFP or cryoprecipitate in this setting although the use of blood product support may have a role in patients with bleeding and prior to interventions with clinically significant bleeding risk.

Key practice point

In liver disease the standard coagulation tests may be misleading and do not reflect bleeding risk. They should generally not be used alone to trigger transfusion with FFP or cryoprecipitate.

3.4.5 Warfarin anticoagulation reversal

Most children on long-term warfarin therapy have underlying congenital heart disease. Emergency reversal of over-anticoagulation is occasionally required to treat major bleeding, or bleeding in critical sites. High quality evidence from adult studies shows that FFP produces suboptimal correction of coagulation defects compared with PCCs (Makris *et al*, 1997; Goldstein *et al*, 2015). A dose of 25–50 iu/kg of a four factor PCC (containing factors II, VII, IX and X) together with vitamin K administration is now the treatment of choice (BCSH, 2011a). FFP should only be used if four factor PCC is not available. Treatment options for bleeding in association with use of new oral anti-coagulants are beyond the scope of this guideline.

Recommendation

FFP should not be used for urgent warfarin reversal unless four factor prothrombin complex concentrate is unavailable (1B).

3.4.6 Vitamin K deficiency bleeding

See Section 2.4.4.

3.4.7 Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome

TTP, with pathological features caused by microangiopathic thrombosis, results from a deficiency of the ADAMTS13

enzyme. This may be secondary to anti-ADAMTS13 antibodies, or due to an inherited deficiency in congenital TTP (Loirat *et al*, 2013).

Acquired TTP

TTP should be considered in the differential diagnosis in children presenting with microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. It is a serious disease with a high mortality if not treated promptly (BCSH, 2012b). Urgent (within 6 h) plasma exchange (PEX) using solvent detergent (SD) treated FFP is mandatory and is superior to plasma infusion alone. Methylene blue (MB) FFP has been associated with a need for increased numbers of PEX and with a longer hospital stay in TTP (de la Rubia *et al*, 2001; del Río-Garma *et al*, 2008). Urgent PEX is also recommended for some forms of atypical HUS although not routinely for diarrhoea-associated HUS (Schwartz *et al*, 2016) or pHUS (Spinale *et al*, 2013; Schwartz *et al*, 2016;). It may be considered for HUS with cerebral symptoms. Note that platelet transfusions are generally avoided in TTP or HUS unless there is life-threatening bleeding due to concerns that they may worsen the clinical situation (see Section 3.3).

Congenital TTP

Congenital TTP is a rare disorder that can present at any age (e.g. triggered by pregnancy), with more severe forms usually presenting early in life. Congenital TTP is managed with either SD FFP or with intermediate purity FVIII concentrate, which contains ADAMTS13 (e.g. BPL 8Y) and which may also be used for prophylaxis. For further information see BCSH guidelines (BSCH, 2012b).

Recommendations

1 **Urgent plasma exchange with SD FFP is indicated for TTP (1B) and some forms of atypical HUS (2C).**
2 **SD FFP infusion (in the acute phase) and intermediate purity Factor VIII (e.g. BPL 8Y) should be used to treat congenital TTP (1C).**

3.4.8 Inherited bleeding disorders

Where specific coagulation factor concentrates are available, these are the treatment of choice for patients with inherited bleeding disorders. FFP and cryoprecipitate should not be used (United Kingdom Haemophilia Centre Doctors' Organization [UKHCDO], 2008; BCSH, 2014b). Factor (F) V deficiency is the only single factor deficiency where a factor concentrate does not currently exist; in this situation, pathogen-inactivated plasma, e.g. SD FFP is recommended. This can also be used together with FVIII concentrate in the management of combined FV & FVIII deficiency. In FXI deficiency, pathogen-inactivated plasma FFP may be preferred in certain situations due to prothrombotic risks associated with FXI concentrate (Pike & Bolton-Maggs, 2015). This is less likely to be an issue in children where the overall risk of thrombosis is low but SD FFP may be used if replacement therapy is required urgently and FXI concentrate is not immediately available.

In certain situations, while awaiting confirmation of a suspected inherited factor deficiency, FFP may be used for acute management. In suspected haemophilia, doses of 20 ml/kg are often recommended but will only result in a relatively small increase in the FVIII or FIX and should not be used once a specific factor deficiency is confirmed.

Recommendations

1 **FFP should not be used in the management of inherited factor deficiencies other than in a few exceptional circumstances where specific factor concentrates are not available (1B).**
2 **Cryoprecipitate should not be used for congenital hypofibrinogenaemia unless fibrinogen concentrate is unavailable (1C).**

3.5 Granulocytes

In the UK, granulocytes for transfusion are produced using one of two means: by apheresis or as a component derived from whole blood donations (Bashir *et al*, 2008). Granulocyte transfusions may be requested for use in neutropenic haematology/oncology/immunology patients with refractory infection or at high risk of developing severe infection (Strauss, 2012). Most patients prescribed granulocyte transfusions are those with cancer-related neutropenia, who are receiving myeloablative chemotherapy with or without haemopoietic stem cell rescue. Recent studies with variable or promising, but overall inconclusive, results have been reported both in adults (Oza *et al*, 2006; Seidel *et al*, 2008) and children (Sachs *et al*, 2006). The exact role of granulocyte transfusions (whether derived from whole blood or collected by apheresis) therefore remains unclear. In the UK, a recent study reported on the safety of the use of a component derived from whole blood donations, and recruitment included 13 children (Massey *et al*, 2012). The reaction profile was similar to that with other granulocyte components and all the children recovered.

Recommendation

Granulocyte transfusions may be considered for treatment of refractory infections in children with severe neutropenia (2C).

4 Cardiac surgery

Approximately 13% of red cell transfusions to children in the UK are to support cardiac surgery (New *et al*, 2014). The factors contributing to this high blood use include the nature of the surgery and the coagulopathy associated with cardiopulmonary bypass (CPB). Clinically significant bleeding associated with paediatric cardiac surgery may be defined as WHO grade 3–4. Certain congenital cardiac conditions are associated with T-cell immunodeficiency (including Di George syndrome) and, if suspected, irradiated cellular blood components should be provided until the syndrome is excluded by diagnostic testing (BCSH, 2011b).

4.1 Red blood cells

Red blood cells (RBCs) are required during cardiac surgery with CPB, both as part of the priming solution for the bypass circuit to counter the effects of haemodilution and following CPB to replace losses. The primary transfusion threshold for red cells in paediatric cardiac surgery remains the Hb. The optimum Hb thresholds are not clear and there is variation in practice (Mazine *et al*, 2015).

A recent Cochrane review of children requiring surgery for congenital disorders (Wilkinson *et al*, 2014) including 862 patients in 11 RCTs found insufficient evidence to assess the impact of different red cell transfusion strategies due to the small size and heterogeneity of the trials. It is argued that oxygen delivery in cyanotic heart disease is reduced and to compensate for this such children require a higher Hb than children with non-cyanotic heart disease. The evidence to support this is limited and does not take into account the multiple compensatory physiological mechanisms that help support adequate oxygen delivery in progressive anaemia and desaturation (Wang & Klein, 2010). However current practice is that children with cyanotic heart disease are treated differently to those with non-cyanotic disease (Du Pont-Thibodeau *et al*, 2014).

It is recommended that red cells for neonates and infants receiving large volume red cell transfusions for cardiac surgery should be used before the end of Day 5 (see Sections 2.2.3 and 7.1.5), although there is not strong evidence to support this strategy. Electrolyte changes, such as hypocalcaemia, must be closely monitored and corrected and there is concern that older or irradiated blood might be associated with cardiac arrest at the start of CPB in small children due to high serum potassium concentrations. It is also possible that some rare units might have particularly high levels of potassium if the donor has a mutation for familial pseudohyperkalaemia, resulting in red cells that leak potassium more rapidly at the low temperatures of red cell storage (Bawazir *et al*, 2014). If the concentration of potassium in a unit of red cells is high, it is possible to wash the red cells in a cell saver prior to addition to the circuit (Hall *et al*, 1993; Lee *et al*, 2014).

Cardiopulmonary bypass

The volume of red cells required in the priming solution depends upon the mismatch between the volume of the circuit and the weight of the child, together with the pre-bypass and target Hb. Although experience with miniaturized circuits is reported, reducing the need for red cells, (Redlin *et al*, 2012) their use is uncommon and currently red cells are usually required for priming standard circuits for neonates.

For non-cyanotic children during CPB, an RCT reported by de Gast-Bakker *et al* (2013) showed that a transfusion threshold of 80 g/l was safe both on bypass and in the postoperative period for low risk non-neonatal patients. During CPB in children with cyanotic heart disease, better outcomes were shown in three small randomized trials including neurodevelopmental outcome at 1 year when the haematocrit on bypass was maintained above 0·25 (Hb approximately 85 g/l) (Jonas *et al*, 2003; Newburger *et al*, 2008; Wypij *et al*, 2008). Adult evidence (Curley G. *et al*, 2014) may also be used to guide red cell usage in low risk patients. However, the current level of evidence in children precludes making firm recommendations.

There is no evidence to guide appropriate transfusion thresholds in neonates during CPB; current practice generally follows the guidance for cyanotic non-neonatal patients.

Post-cardiopulmonary bypass

Data derived from cardiac patients in the TRIPICU study showed that in 125 stable non-neonatal, non-cyanotic patients, a restrictive red-cell transfusion strategy with a threshold of 70 g/l in the postoperative period was not associated with a statistically significant change in rates of organ dysfunction when compared with a more liberal threshold of 95 g/l (Willems *et al*, 2010). de Gast-Bakker *et al* (2013) compared a restrictive (80 g/l) and liberal (108 g/l) transfusion strategy in non-neonatal, non-cyanotic children undergoing cardiac surgery and found that the restrictive group had a shorter length of hospital stay, suggesting that a threshold of 80 g/l throughout the perioperative course was safe. It remains unclear whether a higher threshold for transfusion is required for unstable non-cyanotic patients (Lacroix *et al*, 2012).

In a small postoperative study of 60 children with single ventricle (cyanotic) physiology, 30 were randomized to a restrictive strategy (threshold 90 g/l) and 30 to a liberal strategy (130 g/l) (Cholette *et al*, 2011). The two groups showed no difference in outcomes including lactate concentration, arteriovenous and arteriocerebral oxygen content and length of hospital stay. This suggests that a transfusion threshold of 90 g/l may be safe for stable cyanotic children following cardiac surgery but the study was small and insufficient to support a recommendation.

In unstable or actively bleeding cyanotic or non-cyanotic patients in the post-CPB period, in addition to Hb, overt

signs of inadequate oxygen delivery, such as tachycardia, hypotension, a rising lactate concentration or decreasing mixed venous or cerebral regional oxygen saturation, may provide additional information to support transfusion (Guzzetta, 2011).

Recommendations

1 **There is insufficient evidence to make a recommendation regarding an appropriate transfusion threshold during cardiopulmonary bypass (CPB) for non-cyanotic or cyanotic patients (2C).**
2 **For stable children with non-cyanotic heart disease, a restrictive transfusion threshold of 70 g/l following CPB is recommended (2B). There is insufficient evidence to make a recommendation for children with cyanotic heart disease (2C).**
3 **In neonates (both cyanotic and non-cyanotic) or actively bleeding or unstable children following CPB, a higher Hb threshold may be appropriate (see Table I for general neonatal guidance), and signs of inadequate oxygen delivery can provide additional information to support transfusion (2C).**
4 **Blood used for cardiac surgery in neonates and infants should be used before the end of Day 5 (see Section 2.2.3) (1C)**
5 **Potassium concentrations should be checked in the bypass fluid before connecting to the patient to ensure that they are within the normal range. Individual paediatric cardiac surgery units should have their own internal guidance on the maximum acceptable potassium concentration in the circuit prior to commencing CPB, and measures to adjust the level if necessary, such as washing or ultrafiltration of the prime. If the bypass circuit potassium levels are noted to be unusually high such that they cannot be adjusted by normal procedures, an alternative red cell unit should be requested (with appropriate specification dependent on availability if the situation is urgent) (1C).**

4.2 Cell salvage

Cell salvage including collection and washing of the residual bypass circuit contents is commonly used during cardiac surgery in both neonates and children. In addition to reducing allogeneic transfusion in the first 48 h following surgery (Cholette *et al*, 2013), cell salvage is associated with a lower incidence of postoperative renal failure, a higher postoperative haematocrit and no increase in chest tube drainage (Ye *et al*, 2013). The transfusion thresholds described in the previous section apply to allogeneic blood; cell salvage is frequently reinfused in theatre at Hbs above these thresholds in order to reduce subsequent allogeneic transfusion.

Key practice point

It is reasonable to re-infuse salvaged cells even if the patient's Hb is above the recommended transfusion threshold as this may reduce subsequent allogeneic transfusion and additional donor exposure. The risks are low, but adequately trained staff are essential.

Recommendation

Red cell salvage is recommended for all neonates and children undergoing cardiac surgery with CPB (1B).

4.3 Antifibrinolytics and other strategies to reduce blood loss

Tranexamic acid significantly reduces bleeding and blood transfusion following paediatric cardiac surgery (Zonis *et al*, 1996; Chauhan *et al*, 2003; Faraoni *et al*, 2012), with most evidence from patients with cyanotic heart disease. However, although several studies are reported, most are small and poorly designed with a marked variation in dosing (from 10–100 mg/kg as a bolus dose, 0–200 mg/kg during CPB and 0–15 mg/kg/h). A systematic review found that due to the heterogeneity of the studies, the benefit to risk ratio of tranexamic acid for paediatric cardiac surgery could not be adequately defined, and therefore current evidence to support its routine use in these patients is weak (Faraoni *et al*, 2012). The optimum dose of tranexamic acid for different age groups remains unclear, but recent pharmacokinetic analysis (Wesley *et al*, 2015) suggests that a bolus dose should be followed by an infusion. In view of increasing evidence to support the use of tranexamic acid in non-cardiac surgery, there is an urgent need for large well-designed randomized trials to also clarify its possible role in cardiac surgery.

Aprotinin, an alternative antifibrinolytic agent, also reduces bleeding and blood transfusion following paediatric cardiac surgery (Arnold *et al*, 2006; Breuer *et al*, 2009; Guzzetta *et al*, 2009). The adverse outcomes reported in some adults, including acute kidney injury, have not been reported in children. A recent multicentre comparative analysis of aprotinin and other antifibrinolytics in 22 258 children reported that aprotinin vs no drug was associated with a reduction in bleeding, reoperation and mortality without an increase in the need for dialysis (Pasquali *et al*, 2012). There was, however, no observed benefit of aprotinin in neonates. Conversely, tranexamic acid vs aprotinin showed improved benefits for tranexamic acid in all ages including in neonates, apart from a re-do sternotomy subgroup. This large but observational study was limited by the lack of data on comparative dosing. Overall, UK paediatric cardiac surgery practice in the use of antifibrinolytics is variable due to a persisting lack of clarity on appropriate dosing (Arnold, 2014).

Modified ultrafiltration immediately following separation from CPB has been shown to reduce dilutional coagulopathy, increase Hb, and decrease postoperative bleeding and transfusion (Friesen *et al*, 1997).

Fibrin sealants are increasingly used in paediatric cardiac surgery. There is some evidence from adult studies and a limited number of small randomized controlled trials in children to suggest that these may have some additional benefits in reducing bleeding and blood transfusion following cardiac surgery (Codispoti & Mankad, 2002; Carless *et al*, 2003).

Recommendation

Consider using antifibrinolytic therapy in neonates and children undergoing cardiac surgery at high risk of significant bleeding (1B).

4.4 Haemostasis

Pre-operative haemostasis should be optimised, e.g. by ensuring adequate vitamin K replacement. In addition, children may have been prescribed oral anticoagulants or antiplatelet agents following previous cardiac surgery; these must be discontinued and, if necessary, bridged with unfractionated or low molecular weight heparin (Jain & Vaidyanathan, 2010; Mohanty & Vaidyanathan, 2013). Preoperative prophylactic transfusion of FFP or cryoprecipitate is not indicated for minor coagulation abnormalities, particularly as the patients will be anticoagulated with heparin prior to CPB. If there is post-operative bleeding and the APTT is prolonged it is important to ensure that heparin has been adequately reversed. The recommendations below refer to transfusion for clinically significant bleeding post-CPB.

Cardiopulmonary bypass results in reduced platelet numbers and impairs platelet function, predisposing to increased postoperative bleeding. If the patient is bleeding and a surgical source cannot be identified platelet transfusions are frequently prescribed when the platelet count is less than 100×10^9/l (Table III). CPB in neonates and children may result in marked reduction of coagulation factors including fibrinogen, due to haemodilution, loss from the circuit and consumption. In a patient with significant bleeding following cardiac surgery, FFP may be of benefit when the PT is greater than 1·5 times normal. A number of recent studies have correlated fibrinogen levels with blood loss following adult (Kindo *et al*, 2014) and paediatric cardiac surgery (Moganasundram *et al*, 2010; Faraoni *et al*, 2014). A fibrinogen level of 1·5 g/l is commonly used as the transfusion threshold for cryoprecipitate in line with major haemorrhage guidelines (BCSH, 2015). There has been increasing interest in the role of fibrinogen concentrate, but a recent systematic review by Lunde *et al* (2014) concluded the quality of the currently available evidence was insufficient to support this. This guidance may change in the light of future high quality RCTs. Fibrinogen concentrate is not licensed for this use the UK.

Recommendation

For clinically significant bleeding following CPB and platelet count $<100 \times 10^9$/l, PT or APTT >1·5 times midpoint of normal range, fibrinogen <1·5 g/l specific component replacement may be warranted (2C).

4.4.1 The role of point of care testing

Thrombelastometry and thromboelastography may support early appropriate treatment of the coagulopathy associated with CPB and haemorrhage in paediatric cardiac surgery (Moganasundram *et al*, 2010). It remains unclear whether the correlation between thromboelastography and postoperative bleeding is better than with conventional laboratory testing (Pekelharing *et al*, 2014), but results may be available more quickly, allowing earlier intervention. Several small randomized controlled trials have suggested that the development of algorithms based on this technology may reduce blood loss and transfusion, however the predictive value has still not been fully validated, and large scale studies are required (Romlin *et al*, 2011; Nakayama *et al*, 2015). In addition, there are few data on reference ranges for point of care testing in neonates (Chan *et al*, 2007).

Key practice point

Point-of-care testing in paediatric cardiac surgery may support a rational approach to coagulopathy following CPB. Further developments in this area must be supported by a critical evaluation of developing evidence and an on-going programme of audit and quality assurance.

5 Major haemorrhage

5.1 Massive blood loss in infants and children

Massive blood loss (MBL) related to trauma is uncommon in children. Major bleeding is more common in the surgical setting. The total blood volume in children ranges from 90 ml/kg in term infants down to 70–80 ml/kg in later childhood/adolescence. For simplicity, a figure of 80 ml/kg could reasonably be applied for all children. Massive blood loss may be defined as either 80 ml/kg in 24 h, 40 ml/kg in 3 h or 2–3 ml/kg/min. In clinical practice, haemodynamic changes compatible with hypovolaemia accompanying evidence or suspicion of serious haemorrhage are the usual triggers.

The principles of management of massive blood loss in adults should be broadly applied to the care of children (Spahn *et al*, 2013; BCSH, 2015). There is little evidence available to guide paediatric care (Diab *et al*, 2013).

Key principles in MBL are:

1 Early recognition of children at risk of MBL using clinical parameters
2 Education of staff to understand when to activate/trigger the local major haemorrhage protocol and to seek specialist assistance as appropriate
3 Active resuscitation and control of bleeding
4 Seek specialist assistance (with paediatric expertise)
5 Rapid provision of O D-negative or group-specific red cells
6 Prescribe all transfused components in ml/kg bodyweight (for children <50 kg) and not as units
7 Anticipate and treat coagulopathy and thrombocytopenia in trauma with early use of FFP and consideration of platelets and cryoprecipitate in on-going bleeding
8 Use tranexamic acid in trauma (see below)
9 Avoid hypothermia, hypocalcaemia, acidosis and hyperkalaemia

Good communication with the hospital transfusion laboratory is essential and should be clearly defined in a massive haemorrhage protocol (MHP), which should include a section adapted for children. Education about the core principles of MHP activation and management in children should be targeted at paediatric trainees and staff in Emergency Departments and theatres. Audit and review of management of all cases of massive blood loss/activation of protocols in children should be planned.

5.2 Component use

Transfuse age-appropriate components where possible (Section 7). If a child has life-threatening haemorrhage and no suitable paediatric component is available, then the next best adult component should be provided until the situation is stabilized or the laboratory receives age-appropriate components.

Because unit sizes vary for children, the recommended component ratios should be pragmatically given on a volume basis rather than as units. Initial immediate transfusion of 20 ml/kg RBCs should be given (up to four adult units), O D-negative or ABO and D-specific. The recent Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) RCT (Holcomb *et al*, 2015) in adults reported that there was no difference in overall survival between early administration of plasma, platelets and RBCs in a 1:1:1 ratio and in a 1:1:2 ratio. However fewer patients in the 1:1:1 group died due to exsanguination by 24 h. Therefore, early use of FFP and platelets should be considered prior to the results of coagulation tests where bleeding is on-going.

A ratio of at least 1 FFP:2 RBC is recommended in early resuscitation of major haemorrhage (in major trauma clinicians may consider aiming for a ratio of 1 FFP:1 RBC). Platelets and cryoprecipitate must be considered if active bleeding persists after initial resuscitation. Appropriate aliquots to be transfused are as follows:

- RBCs 20 ml/kg aliquots (maximum four adult units), O D-negative or ABO and D-specific (ideally, cross-matched)
- FFP in 20 ml/kg aliquots (maximum four adult units)
- Platelets in 15–20 ml/kg aliquots (maximum one adult therapeutic dose) to be considered after every 40ml/kg RBCs
- Cryoprecipitate 10 ml/kg (maximum two pools)

These aliquots should be repeated in recommended ratios as necessary until bleeding is controlled. Ratios should be modified accordingly once laboratory parameters are available. The therapeutic aims should be Hb 80 g/l, fibrinogen >1·5 g/l, PT ratio <1·5, platelet count >75 $\times$ 10^9/l. Careful monitoring for adequacy of resuscitation and for circulatory overload is essential. See Appendix 4 for an example of a major blood loss algorithm.

Key practice points

1 *Each hospital that may encounter children with massive blood loss should agree and operate a dedicated children's massive blood loss guideline and algorithm including transfusion and clinical guidance. Surgical and trauma teams should have immediate access to emergency RBCs and transfusion laboratories should have plans in place to ensure rapid provision of components for children.*
2 *Early use of FFP, platelets and cryoprecipitate is recommended in order to reduce coagulopathy and thrombocytopenia.*

Early use of tranexamic acid has been shown to reduce mortality in adult trauma (CRASH-2 trial collaborators, 2010) and this beneficial effect may also apply in children. An initial dose of 15 mg/kg (maximum 1000 mg) intravenously over 10 min given as soon as possible and within 3 h of trauma, followed by 2 mg/kg/h for at least 8 h or until the bleeding stops has been recommended by the RCPCH and the Neonatal and Paediatric Pharmacists Group (RCPCH, 2012).

Recommendation

Tranexamic acid should be used where massive blood loss is anticipated in children presenting with major traumatic injuries, according to the timing and dosage recommended by the Royal College of Paediatrics and Child Health (2012) (Grade 2C).

6 Prescription and administration

The recommendations of the BCSH Guideline on the administration of blood components (BCSH, 2009) should be followed. However, there are a number of circumstances that may place infants and children at particular risk and where particular care is required. The Serious Hazards of Transfusion reporting scheme has shown that there were a disproportionate number of transfusion errors in the paediatric age group (Stainsby *et al*, 2008) and the paediatric red cell

National Comparative Audit of Blood Transfusion reported a significant proportion of transfusions prescribed as units, and with volumes transfused >20 ml/kg (New *et al*, 2014). Education should be targeted at all clinical staff on all paediatric wards.

6.1 Key areas for caution in paediatric administration and prescribing

6.1.1 Patient identification

There may be confusion over maternal and baby samples, multiple births (especially using consecutive identification numbers), babies without first names, failure to apply wristbands, removal of wristbands by children and/or parents or during procedures and failure to make wristbands accessible during surgery (note alternatives may be used (National Comparative Audit of Blood Transfusion, 2011)). For these reasons, the practice of requiring a second sample collected at a different time for confirmation of the ABO group of a first time patient prior to crossmatching is advocated (BCSH, 2013b; see also Section 8.2.3) unless secure electronic patient identification systems are in place, as long as this does not delay urgent transfusion. In order to reduce neonatal blood testing it is acceptable to use a cord sample as the first grouping sample.

6.1.2 Transfusion volumes

In order to prevent over-transfusion of blood components all prescriptions should be ordered and prescribed in millilitres rather than units although some hospitals may have local protocols allowing transfusion in units for larger, older children. The maximum prescribed volume should not be greater than the volume for equivalent adult transfusions. See Appendix 1 for further details including transfusion rates.

Calculation of red cell transfusion volume in non-bleeding patients

In a non-bleeding infant or child it is important to take into account the pre-transfusion Hb in relation to the transfusion threshold, and it is recommended that a post-transfusion Hb no more than 20 g/l above the threshold be aimed for.

$$\textit{Volume to transfuse}\ (\text{ml}) = \frac{\text{Desired Hb (g/l)} - \text{Actual Hb (g/l)} \times \text{Weight (kg)} \times \text{Factor}}{10}$$

This transfusion formula does not provide a precise prediction of the rise in Hb for a given transfused volume due to variation in the clinical situation and Hct of transfused red cells. Factors between 3 and 5 have been recommended (see New *et al*, 2014). It is reasonable to use a factor of 4 in order to avoid over-transfusion but this should be assessed on an individual patient basis. 4 ml/kg approximates to a one unit transfusion for a 70–80 kg adult, typically giving an Hb increment of 10 g/l (BCSH, 2012a)

Note: the formula has been adapted to the harmonized units for Hb in g/l (previously usually quoted as Hb in g/dl), which requires that the calculation includes a step of division by 10. As this is a change from previous practice, in order to prevent over-transfusion it is recommended that clinicians double-check that the final volume calculated is not more than 20 ml/kg for top-up transfusions.

Blood components will be provided by hospital transfusion laboratories as units, and it is good practice to liaise with the laboratory in order to ensure that donor exposure is minimized and that the volume ordered and prescribed is not above the maximum normally prescribed for an adult in a similar situation e.g.

- Platelets – 1 pack (approx. 200 ml for apheresis platelets)
- Red cells – 1 unit (approx. 280 ml) for a paediatric top-up transfusion

  Note: this is particularly relevant for children >50 kg in weight.

Consideration should be given to a dedicated prescription chart for blood components in neonatal units and paediatric wards, allowing for the inclusion of prompts for correct prescribing and space for recording multiple units of blood for a single transfusion episode.

Key practice points

1 *Hospitals should have clear guidelines on transfusion thresholds for different paediatric patient groups.*
2 *Hospitals are recommended to develop paediatric prescription charts to aid correct prescribing of blood components.*
3 *Monitoring during the transfusion process is essential, especially as neonates and younger children may be less able to communicate symptoms of a transfusion reaction.*

Recommendations

1 Prescription of blood components for paediatric transfusion should be in millilitres unless there are local risk-assessed protocols for prescribing in units for older children, and the maximum volume should not be greater than prescribed for adults (1C). Prescribers must take particular care in calculating paediatric transfusion volumes using a transfusion formula, noting particularly the recent changes to reporting Hb (1C).

2 As for recommendations in adults (BSCH, 2013b), a second sample collected at a different time should be tested for confirmation of the ABO group of a first time patient prior to transfusion unless secure electronic patient identification systems are in place, as long as this does not delay urgent transfusion (1C).

6.1.3 Consent

Formal signed consent by the patient (or parent/carer) is not required for blood transfusion (SaBTO [Advisory Committee on the Safety of Blood, Tissues and Organs], 2011), but the issues surrounding transfusion must be discussed with the parent/carer and patient (where age-appropriate) and valid consent taken and documented prior to transfusion wherever possible (Akinkugbe *et al*, 2016). Parent/child information leaflets are published by NHSBT (http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets). The British Association of Perinatal Medicine recommends formal written consent for neonatal exchange transfusion (Section 2.2.1).

For children whose parents refuse to consent to transfusion, for example Jehovah's witnesses, a full and timely discussion between the consultant and the family is crucial. The discussion should include optimising any cardiovascular or respiratory disease, investigation and correction of anaemia, and nutritional advice including information on ensuring adequate iron in the diet. Other measures are use of erythropoietin and iron therapy where appropriate to maximize the Hb, stopping non-steroidal anti-inflammatory drugs between 10 d and 2 weeks prior to surgery, and making a perioperative management plan for children who are on warfarin. Blood components have been administered in order to save life, despite parental refusal or refusal of the child, and individual cases should always be discussed with the Trust/Health Board legal department where possible. For further details see BSCH (2009) and the UK Handbook of Transfusion Medicine (Norfolk, 2013).

Blood components and pre-transfusion testing

7 Blood components and specifications

In the UK, blood components and their specifications are described in the UK 'Guidelines for the Blood Transfusion Services' (http://www.transfusionguidelines.org.uk/red-book) and the NHSBT components portfolio (http://hospital.blood.co.uk/products). In order to reduce the risk of transfusion transmission of vCJD, it is recommended that non-UK plasma from countries with a low risk of vCJD is used for all patients born on or after 1 January 1996 (thus including all children) (http://hospital.blood.co.uk/media/26824/plasma_components_paed.pdf; SaBTO, 2012a) and that apheresis platelets should be provided for this age group whenever possible. MB FFP, MB cryoprecipitate and SD FFP (commercially available) are non-UK sourced and have additional pathogen inactivation steps to reduce the risk of viral transmission due to differences in baseline viral infectivity levels between countries.

7.1 Fetal/neonatal/infant components

Blood components provided for the fetal/neonatal/infant age group in the UK have a particular specification with additional safety features, as these recipients are a vulnerable group due to factors including immunological and neurodevelopmental immaturity and small circulating blood volumes.

Blood components with fetal/neonatal/infant specification are suitable for all recipients under 1 year of age. Individual component types have additional special features, which are described in more detail in Appendix 1. For example, red cells for intrauterine and neonatal exchange transfusion are suspended in citrate-phosphate dextrose to reduce the theoretical risk of toxicity of adenine and mannitol to this age group. Red cells for neonatal exchange transfusion and other large volume neonatal and infant red cell transfusions need to be 'fresh' (used before midnight of Day 5; see Section 7.1.5 and Appendix 1, Table b) in order to reduce the risk of hyperkalaemia.

Fetal/neonatal/infant specification components include the following, details of which can be found in Appendix 1, Tables a–c:

- Intra-uterine transfusion (IUT) red cells and platelets
- Neonatal small volume red cells ('paedipacks')
- Neonatal large volume red cells ('LVT's)
- Neonatal exchange red cells
- Neonatal platelets

Note: MB FFP and MB cryoprecipitate, SD FFP, granulocytes and low titre anti-T fresh frozen plasma may be used for neonates and infants but are not of specific fetal/neonatal/infant specification.

7.1.1 Donor microbiological testing

Components with fetal/neonatal/infant specification are prepared from blood donated by donors who have given at least one previous donation within the previous 2 years, which was negative for all mandatory microbiological markers (unless the components have been treated with a validated pathogen inactivation process). SaBTO https://www.gov.uk/government/groups/advisory-committee-on-the-safety-of-blood-tissues-and-organs) recommended in 2013 that components for infants under 1 year old should continue to be manufactured from donors who have donated at least once previously.

Hepatitis E virus (HEV) transfusion transmission has been reported in the UK and other countries (Hewitt *et al*, 2014). Although transfusion-transmitted HEV infection rarely causes acute morbidity, in some immunosuppressed recipients hepatitis E infection can become persistent. As a result, the introduction of HEV RNA testing of blood components for solid organ and stem cell transplant recipients has been recommended (SaBTO, 2015), and some

Blood Services may also provide these component for infants under 1 year old.

7.1.2 CMV seronegativity

SaBTO (2012b) recommended that CMV seronegative components are required for IUTs and neonates up to 28 d post-expected date of delivery (i.e. 44 weeks corrected gestational age). Once an infant is greater than 4 weeks after their expected date of delivery, they no longer require CMV-negative components. Due to the difficulty in communicating the corrected gestational age for every neonate, issuing CMV-negative components up to 6 months post-delivery irrespective of gestational age would provide a safety net to comply with the SaBTO recommendations. However, all cellular blood components of fetal/neonatal/infant specification for use up to 1 year of age are currently CMV negative, so are compliant with the SaBTO recommendation.

Granulocytes should be CMV negative for neonates up to 28 d post-expected date of delivery or recipients who otherwise require CMV-negative components (see Section 9.3).

7.1.3 Additional antibody screening

Red cell and platelet components with fetal/neonatal/infant specification have been tested by the UK Blood Services and found to be negative for high titre (HT) anti-A and anti-B antibodies. This is in order to minimize risk of haemolysis due to transfusion of ABO non-identical plasma. However, the selection of HT negative platelet components does not totally eliminate the risk of haemolysis. Note that MB FFP and MB cryoprecipitate are not tested for HT antibodies, therefore appropriate group selection of components within the laboratory must also be undertaken (Table IV).

An additional indirect antiglobulin test is performed to screen donor blood for clinically significant red cell antibodies. This is sometimes known as PANTS ('paediatric antibody test') testing.

7.1.4 Minimizing donor exposure

Hospital transfusion laboratories should liaise with neonatal units to develop policies and procedures that help to reduce exposure of recipients to components from multiple donors by using paedipacks (see Section 2.2). For neonatal top-up transfusions paedipacks can be transfused until the expiry date (end of Day 35); ideally, the first paedipack allocation should have a long expiry date so that the multiple packs from the same donor can be used for the neonate as required (see Appendix 5). These measures further reduce the risk of transmission of infectious agents via the blood supply.

7.1.5 Minimizing risk of hyperkalaemia

For some neonatal/infant transfusions 'fresh' blood is recommended in order to reduce the risk of hyperkalaemia: red cell IUTs, neonatal exchange transfusion and neonatal/infant

Table IV. Group selection of plasma-based components.

	ABO group of plasma components to be transfused		
Patient's ABO Group	Platelets	MB FFP & SD FFP‡	MB Cryoprecipitate‡
O			
1st choice	O	O†	O†
2nd choice	A, B or AB	A or B or AB	A or B or AB
A			
1st choice	A	A	A
2nd choice	AB	AB	AB
3rd choice	B*	B‡	B‡
4th choice	O*	–	–
B			
1st choice	B	B	B
2nd choice	AB	AB	AB
3rd choice	A*	A‡	A‡
4th choice	O*	–	–
AB			
1st choice	AB	AB	AB
2nd choice	A*	A‡	A‡
3rd choice	B*	B‡	B‡
4th choice	O*	–	–
Unknown			
1st choice	AB	AB	AB
2nd choice	A*	A‡	A‡
3rd choice	B*	B‡	B‡
4th choice	O*	–	–

FFP, fresh frozen plasma; HLA, Human leucocyte antigen; HT, high titre MB, methylene blue; SD, solvent detergent.

Notes: Platelets

*Tested and negative for HT antibodies: where denoted on the component label this indicates that the component has been tested and contains a low titre of anti-A or anti-B in the plasma.

- Group B or AB platelets may not be available. However, the use of group O platelets for non-O patients should be avoided as much as possible. Platelets should be compatible for D.
- If a patient requires HLA matched platelets, HLA match usually takes precedence over ABO group

Notes: MB FFP, SD FFP and MB cryoprecipitate

†Group O FFP and cryoprecipitate should **only** be given to group O patients.

‡Group compatible plasma should be used wherever possible. MB FFP, SD FFP and MB cryoprecipitate are not tested for HT antibodies. Non-compatible groups should only be used in emergencies when compatible groups are not available.

- AB plasma, though haemolysin free and suitable for patients of any ABO group, should be conserved for group AB patients or emergency transfusions where the patient's group is unknown. Group AB MB cryoprecipitate has limited availability

large volume transfusions. The red cells should be less than 5 d old at the time of transfusion. This means if the collection date is Day 0, the component must be transfused before midnight of Day 5.

Irradiation of red cell units affects the expiry date of the unit due to increases in potassium levels, which occur rapidly following irradiation, reaching levels normally seen at end of storage within a few days post irradiation (Serrano *et al*, 2014). For IUT, exchange transfusions and neonatal/infant large volume transfusions, irradiated red cells must be given within 24 h of irradiation. Red cells for top-up transfusions given at standard flow rates may be used up to 14 d following irradiation (BSCH, 2011b).

Emergency paedipacks intended for neonatal resuscitation (up to 20 ml/kg) should ideally be less than 14 d old to reduce the risk of hyperkalaemia although this is not evidence-based. It is considered good practice for hospitals to have a robust stock rotation mechanism to ensure that the freshest paedipack units are available for resuscitation, especially if they are irradiated.

7.2 Emergency situations

Emergency blood should be available for maternity and specialist neonatal units. Group O D-negative paedipacks should be available for emergency neonatal use. However, O D-negative red cells are incompatible with anti-c/cE and relevant antigen-negative red cells should be used for babies with these maternal antibodies. Two paedipacks should provide a sufficient volume for neonatal resuscitation (up to 20 ml/kg). Standard 'adult' units are not suitable as a standby for neonatal resuscitation except in an extreme emergency as they lack the additional safety specification of neonatal components, including HT negative status.

If maternal and neonatal blood units are stored in the same refrigerator, they should be separated and clearly labelled to prevent accidental selection of the wrong component.

Alternative components in emergency

In emergency situations it may not be possible to meet all the standard neonatal/paediatric specifications and the risks of delays in transfusion have to be balanced against the risk of using components of alternative specification. This includes the use of D-negative units for babies of mothers with non-D antibodies (e.g. anti-c/cE). There should be a locally agreed concessionary release policy for acceptable alternatives for emergency use including a process for communication between the clinical area, the laboratory and the Blood Services (see also BSCH, 2015).

Alternatives are dependent upon the reason for transfusion, availability of components routinely held in stock, timescales for delivery from the Blood Centre and proximity of the local blood storage to the clinical area. A hierarchy for consideration is:

1 ABO compatibility with mother and infant
2 Antigen-negative for maternal antibodies
3 Age of unit
4 Irradiation status
5 CMV negativity: there is acceptance that, in an emergency situation, leucodepleted components may be provided for recipients who would normally receive CMV-negative components
6 A component that satisfies the neonatal specification e.g. multi-satellite packs, MB FFP, HT negative red cells.

It should be noted that in the situation of emergency large volume transfusion for a neonate or infant < 1 year with no neonatal/infant specification red cells available in the hospital, if a non-group O neonate/infant was given an adult group O unit with unknown HT antibody status there is a very low risk of haemolysis from HT antibodies given the small volume of plasma in SAGM units.

Recommended alternatives for emergency intrauterine red cell transfusion can be found in Appendix 3.

Use of D-positive platelets for D-negative female recipients in an emergency

If it is necessary to transfuse a D-negative female recipient with D-positive platelets in an emergency where the appropriate component is unavailable, the recipient should be given anti-D prophylaxis following BCSH recommendations (BCSH, 2014a). This is particularly likely if HPA-1a/5b negative platelets are transfused in suspected NAIT, as HPA antigen negativity would have higher priority than D-type.

Key practice points

1 *Allocate a set of paedipacks when the first neonatal top-up transfusion is requested. They can be used up to 35 d after donation (see Appendix 5).*
2 *Hospital transfusion laboratories should ensure that maternity and neonatal units have access to emergency O D-negative paedipacks (see Section 2.2).*
3 *Hospitals should agree a protocol outlining the hierarchy for acceptable alternatives if specific components are not available in an emergency, and the communication pathway between the clinical area, the hospital transfusion laboratory and the Blood Services.*

Recommendations

1 It is recommended that recipients under 1 year of age be transfused with components with neonatal/infant specification (1C).
2 In order to avoid delays in blood provision, if specific components are not available in an emergency, use pre-agreed hierarchies of alternative components and communication pathways (1C).

8 Key principles for pre-transfusion testing and selection of red cells for neonates and infants less than 4 months of age

8.1 Principles

Fetal and neonatal ABO grouping differs from adult ABO grouping because:

- Fetal/neonatal ABO red cell antigens may be poorly expressed (Klein & Anstee, 2005)
- Due to the naivety of the fetal/neonatal immune system, the corresponding ABO red cell antibodies are not usually well-developed
- Maternal IgG ABO antibodies may be detectable in the fetal/neonatal plasma (Roseff, 2011; Shaikh & Sloan, 2011).

The in-built laboratory double-check for ABO blood grouping cannot be used for fetal/neonatal samples because the red cell antigen (forward) group cannot be confirmed by the plasma antibody (reverse) group.

Fetal/neonatal antibody screening differs from adult antibody grouping because:

- Red cell antibodies are not usually produced within the first 4 months of life even after multiple transfusions (Floss *et al*, 1986; Ludvigsen *et al*, 1987; Klein & Anstee, 2005).
- Maternal IgG antibodies are actively transported across the placenta during the second trimester onwards (Saji *et al*, 1999) providing acquired immunity to the fetus and neonate. These can include clinically significant red cell antibodies and prophylactic anti-D if administered during pregnancy.

Due to these factors, antibody screening of a fetus/neonate represents the maternal antibody status rather than the fetal/neonatal antibody status.

8.2 Pre-transfusion testing for neonates and infants less than 4 months of age

8.2.1 Why use the maternal sample?

Within the first 4 months, wherever possible, samples from both mother and infant should be obtained for initial ABO and D group determination. The antibody screen should be undertaken on the maternal sample when available. A maternal sample is preferred for antibody testing for the following reasons:

- If maternal antibody has bound to fetal cells *in vivo*, the resulting lower concentration of antibody in neonatal plasma could lead to a false negative antibody screen result.
- It is easier to obtain a sufficiently large sample from the mother to allow for screening and antibody identification if required.
- Sample collection from the infant exacerbates the anaemia of prematurity.

The maternal sample should be collected within 3 d pre-delivery or collected post-delivery.

8.2.2 Determining the maternal transfusion history

If the maternal sample is unavailable or the baby was born in another hospital, the maternal group and antibody status and the transfusion history of both mother and baby should be sought from the referring hospital transfusion laboratory. It is vital to remember that sick neonates may be transferred between multiple hospitals: a full transfusion and testing history should be obtained. All information regardless of source should be relayed to the hospital transfusion laboratory, particularly if an IUT has been given, when the infant would require irradiated cellular blood components until 6 months after the expected date of delivery (BSCH, 2011b). Hospitals should use agreed procedures for obtaining clinical information (see Appendix 6 for example proforma), and for management of compatibility testing if the mother remains at a separate hospital following an ex-utero transfer.

8.2.3 Sample testing

All reagents and sample testing processes should be in accordance with BCSH guidelines for Pre-Transfusion Compatibility Testing (BSCH, 2013b).

Investigations on the maternal sample:

1 ABO and D groups (BSCH, 2013b)
2 Screen for the presence of atypical red cell antibodies
3 Identification of the antibody/antibodies if the antibody screen is positive

Investigations on the infant sample:

1 ABO and D forward group: if transfusion is required or likely to be required the infant's blood group should be verified on two samples (unless a secure electronic patient identification system is in place) collected at different times, where this does not impede the delivery of urgent red cells or other components (BSCH, 2013b). One of these samples can be a cord blood sample. Prior transfusion can affect blood group interpretation so any transfusion history needs to be taken into account.
2 Direct antiglobulin test (DAT) should be performed when haemolysis/HDN is suspected or where the mother has had clinically significant red cell antibodies. DATs should not be routinely performed in other situations, including on cord samples sent from neonates of D-negative mothers (BCSH, 2016).
3 In the absence of maternal plasma, screen the infant's plasma for atypical antibodies.

8.2.4 Interpretation of test results and further investigations

Caution when interpreting neonatal ABO grouping is required because fetal or neonatal transfusion prior to sample collection may lead to mixed field results, or misinterpretation of the blood group due to presence of transfused cells. Ensure that the neonate's transfusion history is considered when interpreting and reporting ABO and D grouping.

If the DAT (if indicated) and antibody screen are negative and the confirmation ABO and D groups are not anomalous, then no further pre-transfusion testing is required for 4 months.

If there is an atypical red cell antibody in the maternal or neonatal plasma and/or a positive DAT on the neonate's red cells further investigations should be undertaken to identify the following:

1 Has the maternal antibody the potential to cause HDN?
2 Is the neonate antigen-positive for the maternal antibody?
3 Is there ABO incompatibility between mother and infant?
4 Has the mother received prophylactic anti-D?

When the neonatal DAT is positive an elution may be performed if there is haemolysis and diagnostic uncertainty but is otherwise not generally required. A flowchart for a summary algorithm of testing decisions is shown in Appendix 7. The likelihood of HDN based on the clinical significance of the implicated antibody should be reported and appropriate blood selected for transfusion (see Section 8.3.2).

Note: care must be taken when interpreting a DAT result. It can sometimes be negative during acute haemolysis or be positive for no obvious clinical or serological reason. It may be positive due to anti-D given to D-negative mothers as part of routine antenatal prophylaxis.

8.2.5 Clinical special requirements

Special requirements may be due to clinical factors not known to the laboratory e.g. IUT, immunodeficiency, transplantation. There should be local and shared care procedures for communicating this information to the laboratory (see Appendix 6). The laboratory should have a procedure for recording and managing this information in the form of rules for selection of suitable blood components, e.g. in the Laboratory Information Management System (LIMS).

8.2.6 Neonatal name change

There should be a local policy in place regarding the management of temporary names for neonates e.g. 'Baby' to 'Clare'. The local policy should identify whether a repeat sample is required when the baby's name is changed in the hospital patient administration system.

8.3 Red cell selection for neonates and infants less than 4 months of age

It is important to take the following into consideration:

- Red cells for IUT or neonatal transfusion must be ABO and D compatible with both maternal and neonatal groups, and must be IAT crossmatch-compatible with clinically significant red cell antibodies present in maternal or neonatal plasma.
- If mother and infant are not ABO identical and maternal anti-A or anti-B is present in the infant's plasma, transfused blood that is ABO identical to the infant might haemolyse due to stronger ABO antigen expression on adult donor cells. This is why units that are ABO compatible with both mother and baby must be selected even if the pre-transfusion DAT is negative.
- In general, group O D-negative red cells are used for most neonatal top-up and exchange transfusions. If hospitals use group-specific red cells, most commonly for elective large volume transfusions, they must be ABO and D compatible with both maternal and neonatal groups. It is good practice to use group identical units for elective large volume transfusions in infants in order to minimize use of group O D-negative red cells where possible.
- It is important to minimize donor exposure. Hospital transfusion laboratories may use algorithms that include information about the likelihood of transfusion and age of red cells to guide allocation of paedipacks for top-up transfusion, see Appendix 5 for an example.

8.3.1 Red cell selection: no maternal antibodies present

Select appropriate group and correct neonatal specification red cells. Group O D-negative red cells may be issued electronically without serological crossmatch. If the laboratory does not universally select group O D-negative red cells for neonatal transfusions, group selection should either be controlled by the LIMS to prevent issue of an incorrect ABO group of red cells, or an IAT crossmatch should be performed using maternal or neonatal plasma to serologically confirm ABO compatibility.

8.3.2 Red cell selection: maternal antibodies present

Select appropriate group red cells, compatible with maternal alloantibody/ies. An IAT crossmatch should be performed using the maternal plasma. If it is not possible to obtain a maternal sample it is acceptable to crossmatch antigen-negative units against the infant's plasma.

In cases where paedipacks are being issued from one donor unit it is only necessary to crossmatch the first split as the crossmatch result will be representative of all the satellite units from that donor unit. Subsequent packs from this

multi-satellite unit can be automatically issued without further crossmatch until the unit expires or the infant is older than 4 months. If packs from a different donor are required, an IAT crossmatch should be performed.

Blood that is compatible with maternal antibodies should be provided until the maternal antibody is undetectable in the neonate. However, it is not always practical to repeatedly collect neonatal samples to perform antibody screening so antigen-negative blood crossmatched against maternal plasma is usually provided for up to 4 months. If there is no maternal plasma sample left, repeat testing can either be performed against a fresh maternal or a neonatal sample. If the neonate's antibody screen and DAT become negative, no further crossmatching is required.

Transfusion laboratories should consider how electronic rules for red cell selection and issue are controlled given that the presence of maternal antibody in the neonatal circulation is transient and not neonatal in origin.

Key practice point

It is vital to communicate the need for special transfusion requirements (e.g. irradiated components post IUT) to the laboratory, with shared care hospitals, or internally with other wards.

Recommendations

1 **Obtain the neonatal and maternal transfusion history (including fetal transfusions) for all new neonatal admissions. Obtain a maternal sample for initial testing when possible and use this for crossmatching if required (1C).**
2 **Laboratory control measures are required, ideally controlled by the LIMS, to ensure that units are ABO, D compatible with both mother and baby, and antigen-negative for clinically-significant maternal antibodies (1C).**

8.4 Pre-transfusion testing and red cell selection for infants and children from 4 months of age

For infants and children from 4 months of age, pre-transfusion testing and compatibility procedures should be performed as recommended for adults (BSCH, 2013b). This includes the recommendation that children with sickle cell disease should have extended red cell phenotyping or genotyping (D, C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, M, N, S and s) prior to transfusion and, as a minimum, red cells should be matched for Rh (D, C, c, E, e) and K antigens. It is considered good practice for these same recommendations to apply to children on chronic transfusion programmes, such as those with thalassaemia and bone marrow failure syndromes.

Recipients of allogeneic haemopoietic stem cell transplantations present blood grouping complexities with associated red cell selection problems. Blood component group selection for these patients should be performed as recommended for adults (BSCH, 2013b).

9 Selection of other blood components

For further details see Table IV.

9.1 Selection of platelets

Platelets should match the recipient ABO blood group wherever possible, but it may be necessary to use alternative groups as in Table IV. D-negative paediatric recipients should not receive D-positive platelets because of the risk of allo-immunization to the D antigen. If D-positive platelets must be given in emergency (see Section 7.2), prophylactic anti-D should be considered if the recipient is female.

When NAIT is suspected and results of diagnostic tests are not available, order platelets negative for HPA-1a/5b antigens from the Blood Services until the tests either confirm or exclude the presence of NAIT.

9.2 Selection of plasma

Plasma components should be ABO compatible with the recipient's blood group. In emergencies it may be necessary to use alternative groups, but note that MB FFP and MB cryoprecipitate components are not tested for HT antibodies. Information on HT antibodies is unavailable for SD FFP and ABO compatible SD FFP is recommended (www.octapharma.co.uk).

D compatibility is irrelevant for FFP and cryoprecipitate due to negligible residual red cells. Rules for group and specification of suitable plasma components should be managed by the LIMS (BCSH, 2014c).

9.3 Selection of granulocytes

CMV-negative granulocytes should be selected for CMV seronegative recipients. Granulocytes are irradiated to prevent TA-GvHD. Granulocyte pools are contaminated with RBCs (Hct <0·20) and, as such, should be selected by blood group, crossmatched if necessary or electronically issued based on the same rules as for red cells (for further information see Appendix 1, Table e and Elebute *et al*, 2016).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Author contributions and declarations of interest

HN chaired the writing group and assembled the final draft. All authors took an active role in drafting and reviewing sections of the guidelines and in approving the full guidelines in a series of meetings, discussions and correspondence. The BCSH paid the expenses incurred during the writing of the guidelines. All authors have made a declaration to the BCSH and Task Force Chairs, which may be reviewed on request.

Competing interests

The authors have no competing interests.

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Appendix 1
Component specifications and transfusion volumes

Table a. Fetal/neonatal/infant specification components (general principles).
Suitable for neonates and infants less than 1 year of age. Information is given on those tests that are in addition to those for standard 'adult' components (see http://www.transfusionguidelines.org.uk/red-book).

Component type	Specification	Comments
All	***Donors:***	
	Previously tested donors who have given at least one donation in the previous 2 years, negative for mandatory microbiology markers for the current donation. Some Blood Services are introducing Hepatitis E RNA testing for these recipients in addition to solid organ and stem cell recipients	Reduces risk of infection *Note: imported FFP and cryoprecipitate are not currently from second time donors but they are pathogen inactivated*
	Processing and selection:	
	Components should be tested and shown to be free of clinically significant, irregular blood group antibodies including HT anti-A and anti-B. For this group of recipients an additional indirect antiglobulin test (IAT) is used to screen for clinically significant antibodies, sometimes known as 'PANTS' (paediatric antibody test) tested	Aims to reduce risk of recipient red cell haemolysis, although the risk of haemolysis is low for red cell concentrates in SAGM due to the low volume of plasma *Note: imported FFP and cryoprecipitate are not currently HT or PANTS tested*
	Where specified to be used within a certain time frame, e.g. 'before the end of Day 5', the collection date = Day 0 and the component must be used by midnight on the specified Day	
Red cells	Red cell components for IUTs, neonatal exchange transfusion, and neonatal/infant large volume transfusion are made from blood donations that are processed on Day 0 (not stored at ambient temperature for up to 24 h before processing as for other red cells by some of the UK blood services)	2,3 DPG levels are significantly higher in red cells processed on the day of collection (Wilsher *et al*, 2008), of possible clinical benefit for fetal/neonatal recipients of large volume transfusions
	Haemoglobin S (sickle screen) negative (unless the Blood Centre recommends that screening is unnecessary)	Geographical variation – requirement for provision of haemoglobin S-negative red cells is dependent on prevalence in the population
	K-negative (unless maternal anti-k (cellano) is present, then k-negative must be provided)	Considered best practice to provide K-negative red cells for all recipients in this age group, although the only recommendation is that females of child bearing potential should receive K-negative red cells (BCSH, 2013b)
Red cells and platelets	CMV seronegative	Although all fetal/neonatal/infant red cells and platelets are provided as CMV negative, this is not required for infants >28 d post the expected date of delivery (SaBTO, 2012b) Some Blood Services may provide Hepatitis E RNA tested components for these recipients.
	Irradiated cellular components are supplied for fetal transfusions and specific neonatal recipient groups (BCSH 2011b)	Irradiated to prevent transfusion-associated graft-vs-host disease

Note: see Appendix 1, Tables c and d for general principles of platelet and plasma components for all paediatric age groups. Pathogen-inactivated imported FFP does not currently have a specific neonatal/infant specification.

Table b. Red cell components for fetal/neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
All red cells	*Group and phenotype:* *Less than 4 months of age:* Compatible with maternal and neonatal ABO and D group (usually supplied as group O) and clinically-significant maternal antibodies. *From 4 months of age:* Compatible with recipient's ABO and D group and any red cell alloantibodies.	D-negative red cells should be selected for all D-negative patients less than 18 years old and all females of childbearing age. Fetal/neonatal/infant specification red cells are currently K-negative (Appendix 1, Table a) All females of child-bearing potential should receive K-negative red cells unless unavailable in an emergency (BSCH, 2013b)
IUT Approx unit volume 240 ml	Red cells up to the end of Day 5 Hct 0·70–0·85 Irradiated • shelf-life 24 h post-irradiation In CPD See Section 1.2.1 for administration details	Not stocked in the hospital BT laboratory, special order from the Blood Services • 'fresh' blood, within 24 h of irradiation to reduce the risk of hyperkalaemia • high Hct to minimize number of IUT procedures required • irradiated cellular components are recommended for infants up to 6 months of age post-IUT (BSCH, 2011b) For urgent and emergency situations refer to Appendix 3 for options when specific IUT red cells are not readily available
Neonatal exchange transfusion Approx unit volume 355 ml	Red cells up to the end of Day 5 Hct 0·5–0·6 (NHSBT provide 0·5–0·55) Irradiated • shelf-life 24 h post-irradiation. In CPD Transfusion volume: typically 160 ml/kg (double volume exchange) Transfusion rate: depends on clinical status of baby, discuss with NICU consultant	Not stocked in the the hospital BT laboratory, special order from the Blood Services • tight Hct range provided to reduce the chance of post-exchange transfusion anaemia or polycythaemia • irradiation recommended for all exchanges post- IUT, and for all others unless would cause undue delay (BSCH, 2011b) • 'fresh' blood, within 24 h of irradiation, to reduce the risk of hyperkalaemia • CPD instead of SAGM reduces theoretical risk of toxicity from mannitol and adenine additives (Luban *et al*, 1991) • exchange units contain 100–120 ml plasma with significant coagulation factor activity It is recommended that this component is used only for exchange transfusion of neonates ≤28 d of age, to reduce exposure of older infants to UK plasma and to reduce the theoretical risk of haemolysis from the (usually) group O plasma. If not used, may be reissued for patients born before 1 January 1996
Neonatal/infant small volume transfusions ('Paedipacks') Approx unit volume 45 ml (Six split paedipack from single-donor unit)	Red cells up to the end of Day 35 Hct approx 0·5–0·7 In SAGM additive solution • if irradiated, shelf-life for top-up transfusion 14 d post irradiation Transfusion volume: typically 15 ml/kg (for non-bleeding patients) or use transfusion formula (see Section 6.1.2) Transfusion rate: 5 ml/kg/h	Generally available from hospital BT laboratory stock *Note: specification is the same as for 'LVT' but units are split, and may have been stored at ambient temperature for up to 24 h before processing* • there is no requirement to use red cells before the end of Day 5 for neonatal top-up transfusions but caution should be exercised at high flow rates (Strauss, 2010b). To minimize donor exposure, consider age of red cells when allocating a set of paedipacks to a neonate requiring repeat transfusions • paedipacks are usually transfused on neonatal units; may be used for small infants on other wards • for maternity and specialist neonatal units group O D-negative paedipacks should be available for emergency use. Two paedipacks should provide sufficient volume for resuscitation (up to 20 ml/kg), ideally less than Day 14 to reduce the risk of hyperkalaemia (see Section 7.1.5) • group O D-negative adult emergency units are *NOT* suitable for neonatal resuscitation: they lack the additional neonatal component safety specification • if maternal and neonatal blood are stored in the same refrigerator they must be separated and clearly labelled

Table b. (*Continued*)

Component type	Component details and administration	Comments
Neonatal/infant 'LVT' units Approx unit volume 295 ml	Red cells up to the end of Day 5 if used for large volume transfusion for neonates and infants less than 1 year of age If irradiated, use within 24 h of irradiation for large volume transfusion Hct approx 0·5–0·7 In SAGM additive solution For transfusion volumes and rates in surgery (e.g. cardiac) consult local guidelines	Not stocked in the hospital BT laboratory, special order from the Blood Services Component appropriate for large volume neonatal/infant transfusion e.g. cardiac surgery (BCSH, 2005) • 'Large volume transfusion': typically equivalent to at least a single circulating blood volume (approx 80 ml/kg for neonates) over 24 h or 50% of the circulating volume within 3 h • only contains a small volume of plasma, approx 20 ml (see BCSH, 2005) • if used for small volume top-up transfusion for larger infants, may be used up to end of 35-d shelf-life (14 d post-irradiation)
Red cells for children from 1 year of age (standard 'adult' component) Approx unit volume 280 ml	These are standard red cells in SAGM as provided for adult transfusion (BCSH, 2009) Transfusion volume (see Sections 3.1 and 6.1.2): • generally calculate to take post-transfusion Hb to no more than 20 g/l above the transfusion threshold Transfusion rate 5 ml/kg/h (usual maximum rate: 150 ml/h)	For patients with sickle cell disease, red cells should be Haemoglobin S negative. They should be less than 10 d old, or less than 7 d old for sickle red cell exchange transfusion, although this may not be possible where the patient has multiple alloantibodies. In such situations the freshest available suitable units may be transfused (BCSH, 2016b) For patients with thalassaemia, red cells less than 14 days old are preferred to try to reduce transfusion frequency (Yardumian *et al*, 2016)

Table c. Platelets for fetal/neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
IUT platelets Approx unit volume 75 ml	Group A, D-negative (if ABO D group unknown) or group specific/compatible with maternal antibody HPA compatible with maternal antibody for NAIT (HPA-1a,5b-negative/as required) Obtained by apheresis from a single donor Hyperconcentrated to a platelet count of at least 2000×10^9/l, shelf-life 24 h Irradiated See Section 1.3.1 for administration details	Special order from Blood Services, requiring several days notice • group O platelets should not normally be selected for non-O or unknown group recipients, however the availability of HPA antigen-negative platelets may override ABO group selection considerations • for HPA matched platelets, donors are negative for clinically significant HLA and HPA antibodies • hyperconcentrated to optimise platelet count and minimize volume load Irradiated cellular components are recommended for infants up to 6 months of age post- IUT (BSCH, 2011b)
Neonatal platelets Approx unit volume 45 ml	ABO and D identical or compatible with recipient (see Table IV) HPA compatible with maternal platelet antibody for neonates with NAIT (as for IUT platelets) Obtained by apheresis from a single donor, split into four smaller units Typical transfusion volume: 10–20 ml/kg Transfusion rate: 10–20 ml/kg/h	HPA matched platelets require special order from Blood Services, but HPA-1a/5b-negative usually available 'off the shelf' depending on the geographical location Suitable for neonatal and infant transfusion
Platelets for children from 1 year of age (standard 'adult' apheresis platelets) Approx unit volume 200 ml	ABO and D identical or compatible with recipient (see Table IV) Obtained by apheresis from a single donor where possible Typical transfusion volume: • 10–20 ml/kg for children <15 kg, or a single pack for children ≥15 kg • maximum volume 1 pack Transfusion rate: 10–20 ml/kg/h	These differ from 'neonatal' platelets by not having fetal/neonatal/infant specification. • recipients born on or after 1 January 1996 should be provided with apheresis platelets when possible, as a vCJD risk reduction measure

Table d. FFP and cryoprecipitate for neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
All (apart from low titre anti-T FFP)	Imported from overseas, subject to pathogen inactivation FFP is available either from the Blood Services (single donor, MB treated), or commercially available (pooled, SD treated). Cryoprecipitate is only available from the Blood Services (single donor units, MB treated) ABO compatible plasma should be selected as far as possible (see Table IV). Group O plasma must only be given to O recipients	Plasma (FFP and cryoprecipitate) for use in the UK for those born on or after 1 January 1996 is currently imported from a country with low risk of vCJD in order to reduce the risk of transfusion transmission of vCJD • imported plasma is pathogen inactivated due to different baseline viral infectivity rates in overseas source countries Group AB FFP, though haemolysin-free and suitable for patients of any ABO group, is often in short supply. The D group of plasma components is not relevant
Methylene blue-treated FFP for neonates/paediatrics Approx unit volumes: 55 and 230 ml	Single donor non-UK FFP, MB treated then exposed to visible light to inactivate enveloped and some non-enveloped viruses (Prowse, 2009) Typical transfusion volume: 15–20 ml/kg Transfusion rate: 10–20 ml/kg/h	Available from UK Blood Services • 90% of MB is removed following treatment • MB treatment results in 25–30% reduced factors VIII XI, and fibrinogen, and decreased thrombin generation. However, these are not associated with a reduction in the rate of clot formation or in clot firmness; the clinical significance of the differences is uncertain (Cardigan *et al*, 2009) • MB-treated components are not tested for HT anti-A and anti-B antibodies There is no evidence to guide FFP transfusion volumes for neonates
Solvent detergent FFP Unit volume 200 ml	Pooled FFP from multiple non-UK donors, SD treated, inactivating enveloped viruses. Typical transfusion volume: 15–20 ml/kg Transfusion rate: 10–20 ml/kg/h	Commercially available as 'Octaplas' (Octapharma, Lachen, Switzerland) • the Octaplas LG (ligand gel) product utilizes prion removal technology and is licensed and supplied in the UK • SD plasma has reduced protein S, antitrypsin and antiplasmin and its use has been associated with thrombosis (Prowse, 2009) • a minimum of 0·5 iu/ml of each of the measured factors V, VIII and XI is present;* as it is a pooled product there is less variability than for single donor FFP • administration of Octaplas must be based on ABO-blood group compatibility
Methylene blue-treated cryoprecipitate for neonates/paediatrics Approx unit volume 50 ml, pool volume 280 ml.	This is the cryoglobulin fraction manufactured from imported plasma which has already undergone MB treatment and removal Typical transfusion volume: • 5–10 ml/kg, using single units or pools • 1–2 pools (each containing six donor units) may be used for larger children depending on weight; maximum 2 pools Transfusion rate 10–20 ml/kg/h	Available from UK Blood Services as single units or pools • mean fibrinogen approximately 250 mg/unit, 1273 mg/pool • used mainly for fibrinogen replacement: measure plasma fibrinogen levels following transfusion to confirm the outcome • infusion must be completed as soon as possible and within 4 h of thawing • MB-treated components are not tested for HT anti-A and anti-B antibodies *Note:* group AB MB treated cryoprecipitate has only limited availability (Table IV)
Low titre anti-T FFP	UK sourced FFP, MB treated Group selection, transfusion volumes and rates as for MB and SD FFP above	Available from UK Blood Services, limited supply, requires special order Indicated ONLY for transfusion of neonates with haemolysis following blood component transfusion in whom classical T activation has been demonstrated (Massey, 2011)

*See http://www.octapharma.co.uk/fileadmin/user_upload/Octapharma_UK_New/OPL1202.pdf

Table e. Granulocytes for neonatal/infant/paediatric transfusion.

Component type	Component details and administration	Comments
Pooled buffy coat derived granulocytes.	ABO and D identical and crossmatch-compatible with clinically-significant maternal antibodies as for red cells If ABO compatible but not identical, should be HT negative Irradiated CMV negative for neonates up to 28 d post expected date of delivery or recipients who otherwise require CMV negative	Limited availability (Tues–Sat) requiring at least 24 h notice and Blood Service consultant authorization. Shelf life until midnight on Day 1 Granulocytes derived from buffy coat layer of centrifuged whole blood. 10 donations pooled; each pack contains approximately 1×10^{10} granulocytes (*note: some Blood Services may provide single buffy coat packs)* Buffy coats contain large numbers of both red cells and platelets: • Hct <0·20 so venesection unlikely to be required • Each pack has equivalent of 2·5 adult packs of platelets Irradiated to prevent transfusion-associated graft-vs-host disease due to lymphocyte numbers Not neonatal specification; same component as used for adult transfusion Further information available from the NHSBT Clinical guideline (Elebute *et al*, 2016)
Approx volume of pool 205 ml	Typical transfusion volume: 10–20 ml/kg to a maximum of 2 pools Transfusion rate: suggested 10–20 ml/kg/h	

BT, blood transfusion; CMV, cytomegalovirus; CPD, citrate-phosphate-dextrose; FFP, fresh frozen plasma; Hct, haematocrit; HLA, Human leucocyte antigen; HPA, human platelet antibody; HT, high titre; IUT, Intrauterine transfusion; LVT, large volume transfusion; MB, methylene blue; NAIT, neonatal alloimmune thrombocytopenia; NICU, neonatal intensive care unit; PANTS, paediatric antibody test; SAGM, saline, adenine, glucose, mannitol; SD, solvent detergent; vCJD, variant Creutzfeldt–Jakob disease.

Note: Approximate component volumes from NHSBT components portfolio (http://hospital.blood.co.uk/products). The volumes for components supplied by other UK blood services may vary.

Typical transfusion volumes and rates are given, but may be modified according to individual clinical situations.

Appendix 2
Guideline literature search terms

(((Blood Transfusion[mh:exp]) OR (transfus*[TI] OR pretransfus*[TI] OR retransfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI] OR FFP[TI] OR fresh plasma[TI] OR frozen plasma[TI] OR maternal plasma[TI] OR platelets[TI] OR platelet concentrate*[TI] OR granulocytes[TI] OR cryoprecipitate[TI] OR blood component*[TI] OR blood product*[TI] OR cell salvage[TI] OR blood salvage[TI] OR cell saver*[TI] OR TRALI[TI]) OR (exchange transfusion*[Title/Abstract] OR plasma exchange[Title/Abstract] OR plasmapheresis[Title/Abstract] OR in utero transfusion*[Title/Abstract] OR intrauterine transfusion*[Title/Abstract] OR maternal transfusion*[Title/Abstract] OR placental transfusion*[Title/Abstract] OR partial exchange[Title/Abstract] OR neonatal exchange[Title/Abstract] OR disseminated intravascular coagulation[Title/Abstract] OR DIC[Title] OR T-activation[Title/Abstract] OR coagulopath*[Title/Abstract] OR ((transfus*[Title/Abstract] OR retransfus*[Title/Abstract] OR red cell*[Title/Abstract] OR red blood cell*[Title/Abstract] OR RBC*[Title/Abstract] OR PRBC*[Title/Abstract] OR FFP[Title/Abstract] OR plasma[Title/Abstract] OR platelet*[Title/Abstract]) AND (trigger*[Title/Abstract] OR threshold*[Title/Abstract])))) AND ((Child[mh:exp]) OR (Pediatrics[mh:exp]) OR (Infant[mh:exp]) OR (Adolescent[mh]) OR (low birth weight*[Title/Abstract]) OR (child[Title/Abstract] OR children[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric*[Title/Abstract] OR infant*[Title/Abstract] OR infancy[Title/Abstract] OR neonat*[Title/Abstract] OR newborn*[Title/Abstract] OR babies[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract])))) AND (random* OR blind* OR control group OR groups OR placebo* OR controlled trial OR controlled study OR guideline* OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase)

Appendix 3
Suggested alternatives to IUT red cells for emergency fetal transfusion

1. 'Urgent' situations

Where there is unexpected anaemia requiring an IUT within a few hours, but not an immediate life-threatening emergency

Option (in order of preference)	Notes
1. Irradiated IUT red cells	Generally available from Blood Services in urgent situations within 3-4 h (6 h if out of hours) for fetal medicine units, including transport time, unless there is a maternal antibody that requires sourcing of antigen-negative blood.
2. Irradiated neonatal exchange red cells	If IUT red cells unavailable/take longer than clinically acceptable and neonatal exchange units more readily available *NB* • Hct is lower than standard IUT red cells so post transfusion Hb may be lower • still in CPD like IUT red cells

N.B. If neonatal exchange red cells are unavailable (rarely) or take longer than clinically acceptable it is reasonable to request an urgent irradiated paedipack. Blood Services clinicians are available for discussion.

2. 'Emergency' transfusions

Requiring immediate IUT in order to prevent fetal death

Option (in order)	Notes
1. Irradiated paedipacks	Very few hospitals in the UK are able to irradiate blood components on site, therefore consider ordering irradiated paedipacks on standby near FMU/Labour Ward for suspected high risk cases. *NB* • Hct is lower than standard IUT red cells so post transfusion Hb may be lower. • use within 24 h from the time of irradiation • should be before the end of Day 5 at the time of irradiation, in line with the large volume neonatal transfusion recommendations. • suspended in SAGM, not CPD.
2. Non irradiated paedipacks	As above. Not irradiated, therefore has theoretical risk of TA-GvHD.
3. Adult 'flying squad' blood	Not irradiated, as above Not neonatal/infant specified blood, might not be CMV negative Not necessarily before the end of Day 5 following donation – therefore increased risk of hyperkalaemia

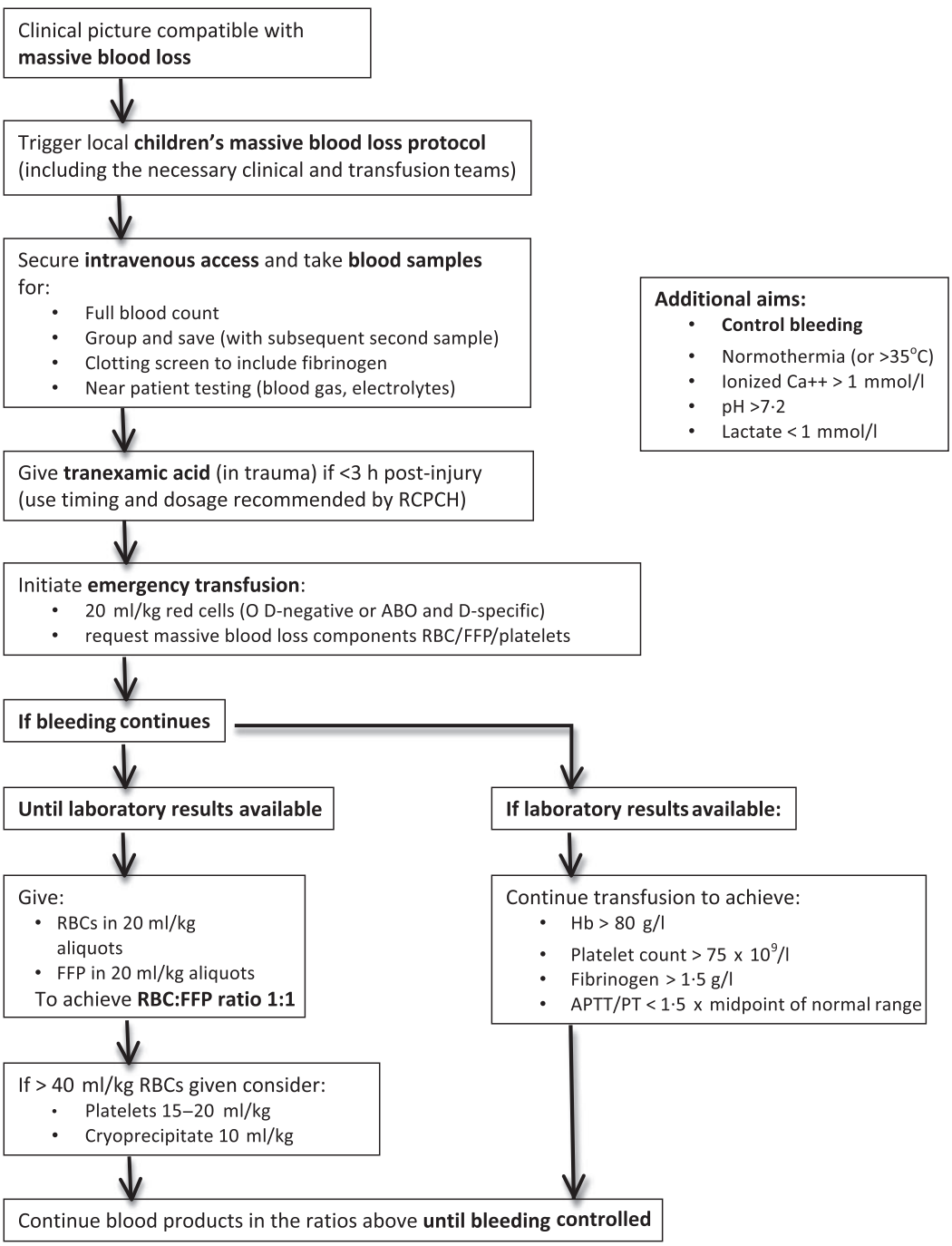
CMV, cytomegalovirus; CPD, citrate-phosphate-dextrose; FMU, Fetal medicine unit; Hb, haemoglobin; Hct, haematocrit; IUT, intrauterine transfusion; SAGM, saline, adenine, glucose, mannitol; TA-GvHD, transfusion-associated graft-versus-host disease.

Hospitals should develop local protocols to clarify the options for IUT components.

NB Maternal blood should not be used for IUT due to the risk of TA-GvHD (as it is not leucodepleted, not irradiated and it is closely related to the recipient)

Appendix 4
Example massive blood loss algorithm

Transfusion management for children (<50 kg) with massive blood loss*



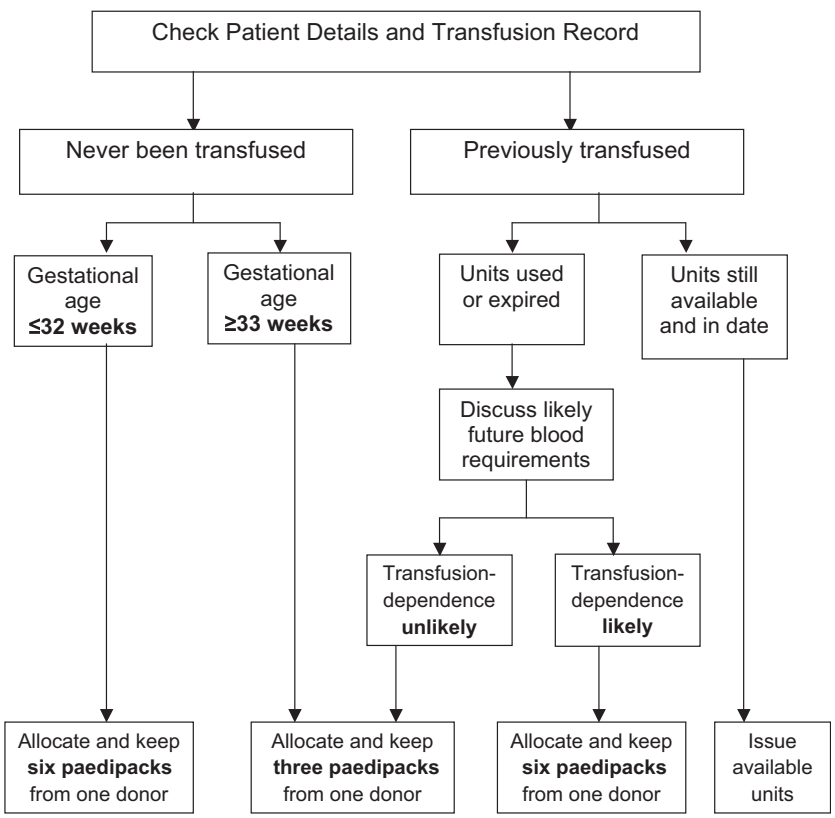
*This is an example algorithm of transfusion-related management of massive blood loss. Local guidelines will need to be developed to take into account current national and local resuscitation standards and surgical and trauma standards.

Algorithm may be adapted for neonatal use. Children >50 kg should be managed according to adult guidelines.

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; PT, prothrombin time; RBC, red blood cell; RCPCH, Royal College of Paediatrics and Child Health.

Appendix 5
Example neonatal paedipack allocation algorithm

This is an example of an algorithm used to allocate paedipacks in order to help reduce donor exposure. It is based on the likelihood of an infant needing repeat transfusion dependent upon gestational age. Gestational age refers to gestational age at birth. When a new paedipack is allocated it should be as fresh as possible in order to maximize the available shelf-life. Local data should be used to help develop the algorithm. Audits should be undertaken periodically to assess its effectiveness in minimizing donor exposure.



Appendix 6
Record of neonate transfusion history enquiry

Part A. Hospital transfusion laboratory to clinical area

Information required from clinical staff to guide safe and appropriate transfusion:
BABY:
Full Name: _____ D.O.B._____
Current Hospital No: _____ NHS No: _____
Birth/Referring Hospital(s): _____ Hospital No: _____
Transfused? YES/NO If yes, details:_____
IUT red cells/platelets? YES/NO If yes, details:_____
Any additional Special Requirements e.g. Irradiated, HPA matched platelets? YES/NO
If yes, details:_____
Gestational age: _____ to assist paedipack allocation (Appendix 5)

MOTHER:
Full Name: _____ D.O.B._____
NHS No: _____
Birth/Referring Hospital(s): _____ **Hospital No:** _____
Any known antibody results from other hospital _____
Details completed by (BMS): _____
Information provided by (clinician's name): _____
Time: _____ Date: _____

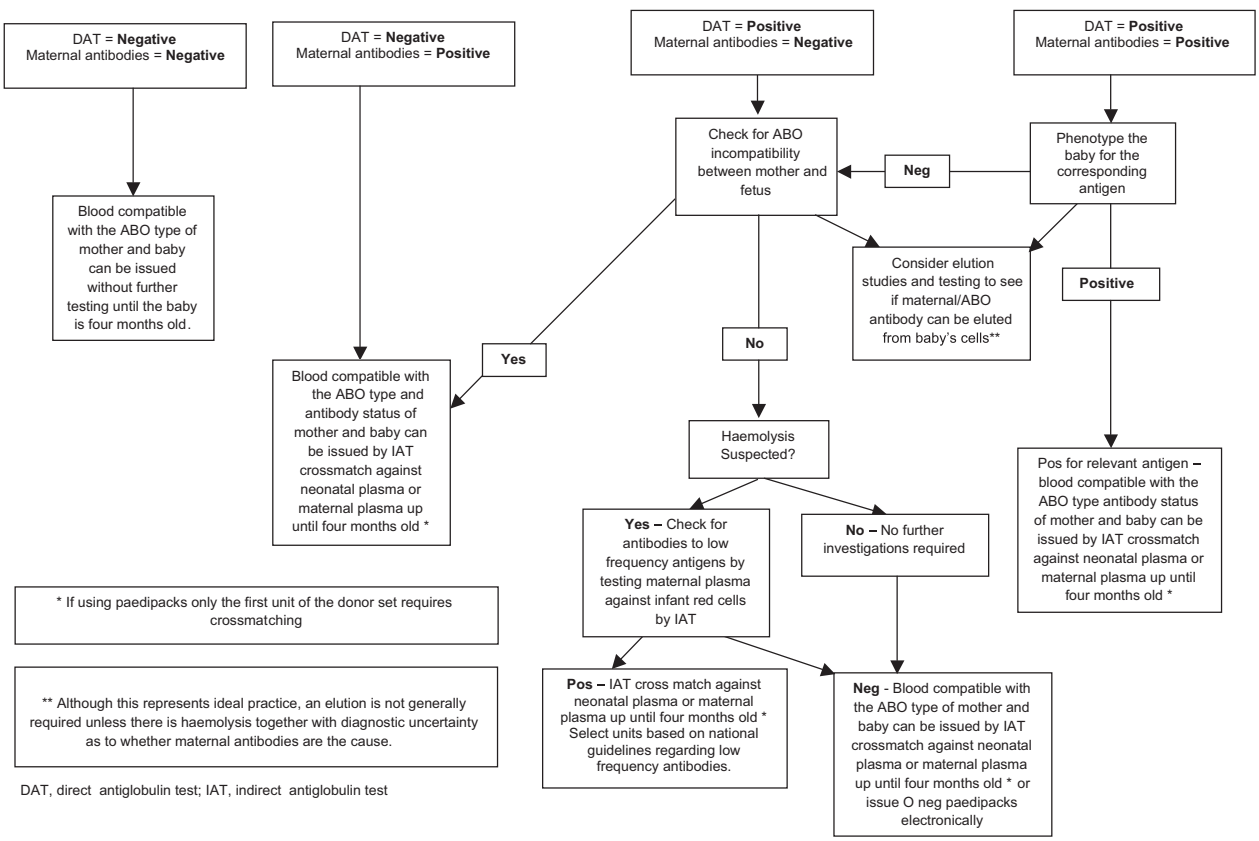
Part B. Hospital transfusion laboratory to hospital transfusion laboratory

BABY:
Full Name: _____ D.O.B._____
Current Hospital No: _____ NHS No: _____
Birth/Referring Hospital: _____Originating Hospital No: _____
Group: _____ DAT Result: _____
Transfused YES/NO If yes, no. of units given_____ Group of units _____
IUT given YES*/NO
***Use IRRADIATED** must be added to the baby record in the LIMS IMMEDIATELY.
Special Requirements: YES/NO If yes, details:_____

MOTHER:
Full Name: _____ D.O.B._____
NHS No: _____
Referring Hospital(s): _____
Original Hospital no. (if known)_____
Group: _____ Antibody history: _____
Transfusion History: _____
Special Requirements: YES/NO If yes, details:_____
Name of BMS in BT at Referring Hospital: _____
Details recorded by (BMS): _____ Time: _____ Date: _____

Note: If IUT or post-delivery transfusion might have occurred at more than one hospital, each hospital transfusion laboratory will need to be contacted in order to obtain full transfusion history.
BMS, Biomedical Scientist: BT, blood transfusion laboratory; DAT, direct antiglobulin test; HPA, human platelet antibody; IUT Intrauterine transfusion.

Appendix 7
Algorithm for compatibility testing for a neonate



* If using paedipacks only the first unit of the donor set requires crossmatching

** Although this represents ideal practice, an elution is not generally required unless there is haemolysis together with diagnostic uncertainty as to whether maternal antibodies are the cause.

DAT, direct antiglobulin test; IAT, indirect antiglobulin test