How we decide when a neonate needs a transfusion

Vidheya Venkatesh, Rizwan Khan, Anna Curley, Helen New and Simon Stanworth

1 Neonatal Intensive Care Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, 2 Department of Paediatrics, Imperial College Healthcare NHS Trust/National Health Service Blood and Transplant, London, and 3 Department of Haematology, National Health Service Blood and Transplant/Oxford University Hospitals NHS Trust, Headington, Oxford, UK

Summary

The decision to transfuse a neonate can be approached by addressing a series of questions that cover the cause of anaemia, alternatives to transfusion, the need for transfusion and the risks. Recent clinical trials of red cell transfusions have started to inform evidence-based transfusion practice, but have raised uncertainties about neurological outcomes when policies advocating use of fewer red cell transfusions at lower haemoglobin concentration (Hb) thresholds were tested. Red cell transfusions should be considered when the Hb <120 g/l for premature neonates requiring mechanical ventilation support, with lower thresholds applying for oxygen-dependent neonates not requiring ventilation or for late anaemia (Hb <70–100 g/l, depending on gestational and post-natal age). There is no recent high quality evidence to inform thresholds for prophylactic platelet transfusions in stable non-bleeding premature neonates with platelet count levels of 50 × 10⁹/l, although common practice has become more restrictive, using lower safe thresholds for platelet transfusion between 20 and 30 × 10⁹/l. A more appropriate transfusion strategy for fresh frozen plasma (FFP) in neonates is one that emphasizes the therapeutic use of FFP in the face of bleeding, rather than prophylactic use in stable non-bleeding neonates who often have mild to moderate apparent abnormalities of standard coagulation tests, after allowing for appropriate reference ranges.

Keywords: red cell transfusion, preterm, neonates, platelets, plasma.

Background

This review will focus largely on the decision to transfuse red cells to neonates. Despite a long history, extending from the first descriptions of transfusion of blood to neonates in the nineteenth century (Diffenbach, 1828), there remains considerable uncertainty about optimal use of red cell transfusions. Much of our neonatal transfusion practice has evolved over decades without the clinical research scrutiny now demanded in an era of evidence-based medicine. As a general rule, an infant may be transfused when the potential clinical benefit outweighs the risk. However, clinical judgments of the need for transfusion in critically ill neonates are imprecise and vary between clinicians and the value and usefulness of more ‘objective’ measures of the need for transfusion [haemoglobin concentration (Hb), haematocrit (Hct) or measurements of oxygen delivery and utilization] is controversial.

Red cell transfusion remains the only treatment for the majority of cases of neonatal anaemia. As a result, red cell transfusions constitute one of the most common procedures performed in the neonatal intensive care unit (NICU; Sacher et al, 1989; Strauss, 2010). Current studies have reported that about 80% of all infants weighing <1.5 kg at birth will receive at least one red cell transfusion (Widness et al, 1996; Strauss, 2010). Much of this is related to phlebotomy losses associated with the provision of neonatal intensive care in high-risk infants. Despite the frequency with which transfusion is performed in a neonatal setting, many questions about optimal transfusion practice remain unanswered. This review will approach the common dilemmas associated with neonatal transfusion through a series of questions and responses.

What are the causes of neonatal anaemia?

Apart from emergency transfusion for acute bleeding, assessment of the need for a red blood cell transfusion first requires consideration of the cause. Neonatal anaemia, defined as a Hb below the lower limit of the reference range adjusted for age, is common. All infants, term and preterm, experience a decrease in Hb during physiological adaptation to the relative oxygen rich extrauterine environment. There is wide variability in levels of Hb at birth, and these differences are tracked through in the weeks after birth, with minimum concentrations being reached earlier in neonates with lower initial Hb, although the minimum levels recorded appear broadly similar in infants born with widely discrepant Hbs (Stockman, 1983).
In term infants, the drop in Hb may extend from 140–220, to 100–120 g/l by 2–3 months of life (physiological anaemia of infancy). In preterm infants this drop in Hb is more rapid and steep due to additional physiological and iatrogenic factors, such that the Hb nadir may fall to 70–80 g/l (Widness, 2008). Preterm infants have a relatively diminished erythropoietin response to anaemia, and lower plasma erythropoietin levels (Stockman et al, 1977). Higher levels of fetal haemoglobin (Hb F) and reduced levels of 2–3 diphosphoglycerate (2,3 DPG), result in an increased affinity of Hb for oxygen. There is also a decrease in the percentage of precursor red cells in the bone marrow compared with term neonates (Strauss, 2010). Other physiological parameters, such as increased growth velocity and shorter red cell life span, contribute to the anaemia of prematurity, in addition to frequent blood sampling from a smaller total blood volume. Co-existing disease processes and co-morbidities, such as sepsis and inadequate nutrition intake, will also affect the development and persistence of anaemia.

A structured approach to the differential diagnosis of anaemia is important, and includes family and obstetric history and examination (e.g. congenital anomalies, features of intrauterine infection). Diagnostic algorithms may assist in the diagnosis of different causes, which can often be suspected from the maternal and neonatal history, alongside gestational and post-natal age, although anaemia in many critically ill premature neonates reflects multiple aetiologies. Initial evaluation should include red cell indices (mean cell volume), reticulocyte count, direct antiglobulin test, and red cell morphological review. Anaemia can be major and life-threatening or an incidental finding in an otherwise well infant, and the diagnostic and therapeutic approaches will differ for both settings.

Principal causes of anaemia are blood loss (e.g. bleeding and blood sampling), haemolysis (e.g. immune) and impaired red cell production (e.g. following infections, such as parvovirus and cytomegalovirus (CMV), or inherited, such as Diamond-Blackfan anaemia). Some causes of blood loss, such as rupture of the cord only when the umbilical artery pulsations have stopped (Gupta & Ramji, 2002), the optimum time of delayed cord clamping is defined as clamping at what level the infant is held (above or below the mother’s abdomen) prior to clamping (Yao & Lind, 1969; Dixon, 1997; Mercer, 2001). The amount of blood returned to the infant depends on when the cord is clamped and at what level the infant is held (above or below the mother’s abdomen) prior to clamping (Yao & Lind, 1974). A review of six randomized controlled trials (RCTs) in preterm infants <37 weeks gestation involving 111 neonates comparing early cord clamping (at ≤30 s) versus delayed cord clamping (30–120 s) showed a decrease in the need for transfusion favouring the delayed cord clamping group [relative risk (RR) 2.01, 95% confidence interval (CI) 1.24–3.27] with no difference in the Hb at birth or at 24 h of age (Rabe et al, 2004). However a subsequent review reported that neonates with late clamping were at increased risk of experiencing asymptomatic polycythæmia (7 studies, Widness et al, 2005) have also contributed to reducing neonatal phlebotomy losses.

Haemolytic causes of anaemia are varied, and may be immune, intrinsic to the red cell, or mechanical. Alloimmune haemolytic anaemia or haemolytic disease of the newborn (HDN) occurs due to transplacental passage of clinically relevant IgG maternal allo-antibodies which react with antigens expressed on fetal red blood cells. The most common allo-antibodies causing severe haemolytic disease are anti-D, anti-c, and anti-K1. Exchange transfusion is indicated for severe hyperbilirubinaemia (despite phototherapy) and for severe anaemia, using a specific neonatal exchange red cell component in citrate phosphate dextrose anticoagulant (see later). Red cell membrane (e.g. hereditary spherocytosis), enzyme (e.g. G6PD deficiency) and, less commonly, haemoglobin disorders can present with neonatal haemolysis, which may be very severe, including hydrops fetalis although more commonly considered for HDN (Gallagher et al, 1997). Other haemolytic causes include drugs, toxins, and micro-angiopathic anaemia (e.g. extra corporeal membrane oxygenation).

What are the alternatives to red cell transfusion?

As for other critically ill patients, prevention and treatment of neonatal haematitic deficiencies must be considered and included in local guidelines, to cover iron and folic acid supplementation or replacement, particularly for preterm neonates as they have lower stores, although identification of these deficiencies is generally rare in a neonatal population. Delayed cord clamping may reduce the subsequent need for transfusion by increasing the amount of red cells returned to the infant, and local policies should be considered and agreed. While delayed cord clamping is defined as clamping of the cord only when the umbilical artery pulsations have stopped (Gupta & Ramji, 2002), the optimum time of delayed clamping has been a matter of debate (Ceriani Cernadas et al, 2006; Chaparro et al, 2006). It is hypothesized that, during the third stage of labour, a delay in cord clamping allows time for an autologous transfer of an additional 30–60% of fetal blood in the placenta to the infant (Yao et al, 1969; Dixon, 1997; Choudhury, 2001). The amount of blood returned to the infant depends on when the cord is clamped and at what level the infant is held (above or below the mother’s abdomen) prior to clamping (Yao & Lind, 1974). A review of six randomized controlled trials (RCTs) in preterm infants <37 weeks gestation involving 111 neonates comparing early cord clamping (at ≤30 s) versus delayed cord clamping (30–120 s) showed a decrease in the need for transfusion favouring the delayed cord clamping group [relative risk (RR) 2.01, 95% confidence interval (CI) 1.24–3.27] with no difference in the Hb at birth or at 24 h of age (Rabe et al, 2004). However a subsequent review reported that neonates with late clamping were at increased risk of experiencing asymptomatic polycythæmia (7 studies, Widness et al, 2005) have also contributed to reducing neonatal phlebotomy losses.

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403 neonates: RR, 3.82; 95% CI, 1.11–13.21; Hutton & Hasan, 2007).

Routine use of erythropoietin is not recommended. The rationale for the use of erythropoietin can be made on the basis of studies that have shown that plasma erythropoietin levels are decreased in term neonates compared to older children or adults. Plasma erythropoietin is further decreased in preterm neonates (Brown et al, 1983). A systematic review of early erythropoietin administration (<7 d of life) based on 27 studies that enrolled 2219 preterm infants (Ohslosn & Aher, 2006) reported that early erythropoietin reduced the risk of the ‘use of one or more red cell transfusions’ [typical RR; 0.80 (95% CI 0.75–0.86); 16 studies, 1825 infants]. However, it also reported a significant increase in the risk of stage 3 retinopathy of prematurity (ROP) in the early erythropoietin group [typical RR; 1.65 (95% CI 1.12–2.43); 8 studies, 984 infants]. Another review of late erythropoietin administration (>7 d of life) showed a significant reduction in the use of one or more red cell transfusions (Aher & Ohslosn, 2006). By this stage of later use, however, the time period for maximal benefit in terms of red cell usage has passed. Therefore erythropoietin use is restricted to a few specific indications, such as to prevent late anaemia in HDN or Jehovah’s Witness families.

What is the benefit of red cell transfusion?

There is a common assumption that lower Hb represents a valid marker of diminished oxygen carrying capacity and that red cell transfusion will improve tissue oxygenation by increasing red cell mass. Several cohort studies have shown that the increased cardiac output and oxygen consumption seen in a preterm infant with anaemia will be normalized following a red cell transfusion (Stockman & Clark, 1984; Alverson et al, 1988; Hudson et al, 1990; Lachance et al, 1994; Bard et al, 1998). Similarly, several studies have demonstrated a decrease in the number of apnoeic episodes following red cell transfusion (Joshi et al, 1987; DeMaio et al, 1989; Sasidharan & Heimler, 1992; Stute et al, 1995), although similar results have also been obtained following albumin transfusion (Bifano et al, 1992). Red cell transfusion can also improve blood pressure and oxygenation within 12 h in a mechanically ventilated preterm neonate (James et al, 1997).

Randomized controlled trials provide the most robust and direct assessment of the need for an intervention, when compared to no-intervention. RCTs comparing red cell transfusion with no transfusion (or a placebo) would therefore be expected to provide the highest levels of evidence for the absolute need and benefit of red cell transfusion in any subgroup of neonates. In a recent systematic review, only three RCTs were identified that compared outcomes between neonates who received a red cell transfusion and those who did not, or those who received 5% albumin (Venkatesh et al, 2012). All three trials were single centre RCTs with a small sample size and while they reported a significant decrease in the number of transfusions, they did not report on clinically relevant neonatal outcomes (Blank et al, 1984; Bifano, 1988; Meyer et al, 1993). These early studies were composed of a moderately preterm population of relatively stable babies and may not extrapolate to current practice treating extremely preterm infants.

In summary, strong evidence from high quality trials to define the absolute requirement and benefit for neonatal red cell transfusion does not exist, even for particular subgroups such as those of older gestational age. Clinicians considering transfusion need to accept this limitation and to weigh up potential benefits against risks, as red cells transfusions are biological agents (see below). This does not mean to say that red cell transfusions are not warranted in groups of neonates, specifically premature neonates, but that evidence to ‘confirm’ effectiveness does not exist. At a practical level, scrutiny should be applied in particular to older neonates who receive single red cell transfusion top-ups prior to discharge – a not uncommon finding in local audits.

Evidence: what triggers should we use for red cell transfusion?

In clinical practice, our decisions to transfuse red cells will aim to treat a deficiency of red cells associated with symptomatic anaemia due to inadequate tissue oxygenation. But defining critical levels of symptomatic anaemia in neonates is challenging. The Hb is generally applied as a surrogate marker of inadequate oxygen delivery but in the future this may be strengthened by applying better physiological criteria for the direct need for red cell transfusion, such as measures of red cell mass, tissue oxygen saturations or measurements of oxygen delivery. However, some of these methods remain technically demanding and are not widely available outside a research setting (Blank et al, 1984; Ross et al, 1989; Meyer et al, 1993; Brooks et al, 1999). Therefore decisions to transfuse continue to be made at specific levels of Hb (or Hct value), with transfusions repeated to maintain Hb at those thresholds judged best for the clinical condition and outcome of the neonate (Strauss, 2010).

A number of RCTs of different Hb triggers have been undertaken to define safe and effective Hb levels for transfusion (Brooks et al, 1999; Mukhopadhyay et al, 2004; Bell et al, 2005; Kirpalani et al, 2006; Chen et al, 2009; Venkatesh et al, 2012). These trials have used different inclusion criteria and compared different levels of Hb (or Hct) as triggers for red cell transfusion, depending on variables such as postnatal age and requirement for respiratory support. In general, those criteria that describe the application of lower Hb concentrations as thresholds for red cell transfusion are termed restrictive strategies for transfusion, by comparison to liberal strategies, which maintain higher Hb concentrations. Table I summarizes information on the different Hb (or Hct) thresholds evaluated in these trials for red cell transfusion. Those
trials that tested more restrictive and liberal strategies for transfusion would be expected to result in a wider separation of patterns of red cell transfusion – and thereby achieve more divergent levels of Hb at follow up (Bell et al, 2005).

One of the more recent trials that applied and tested more restrictive transfusion threshold criteria (or lower Hbs/Hcts) for babies was a single centre study of 100 neonates, enrolled into different groups based on Hct threshold and respiratory status (Bell et al, 2005). It reported no differences in the length of time of ventilator or oxygen support, length of hospitalization, rate of severe retinopathy of prematurity (ROP), chronic lung disease, or mortality between the two groups. A post hoc analysis of a composite outcome of intraventricular haemorrhage (IVH) and periventricular leucomalacia (PVL) favoured the liberal group (Bell et al, 2005). However a follow up study of this cohort showed that changes in brain volume may favour the restrictive arm (Nopoulos et al, 2011), although this follow up study contained only half of infants originally recruited to the study.

In contrast, the Premature Infants in Need of Transfusion (PINT) study (Kirpalani et al, 2006) was a larger multicentre trial that enrolled 451 extremely low birth weight (ELBW) babies and divided them into restrictive and liberal groups based on their Hb threshold, respiratory status and post natal age. Although this study was of a high quality, the mean Hb difference between the two arms was smaller than the

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants Details of red cell transfusion intervention</th>
<th>Main trial conclusion</th>
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<tbody>
<tr>
<td>Kirpalani et al</td>
<td>Extremely low birth weight (&lt;1.0 kg) infants, randomized up to 48 h of age</td>
<td>RBC transfusions by Hb levels depending on postnatal age and respiratory support showing restrictive versus liberal thresholds (note: capillary Hb thresholds shown here; study used thresholds 10% lower when central blood was sampled) For infants receiving respiratory support (assisted ventilation, continuous positive airway pressure or supplemental oxygen) Postnatal week 1: 115 g/l vs. 135 g/l; week 2: 100 g/l vs. 120 g/l; week 3 until discharge: 85 g/l vs. 100 g/l For infants not requiring respiratory support the triggers were – Postnatal week 1: 100 g/l vs. 120 g/l; week 2: 85 g/l vs. 100 g/l; week 3: 75 g/l vs. 85 g/l</td>
</tr>
<tr>
<td>Bell et al (2005)</td>
<td>Infants of 0.5–1.3 kg birth weight</td>
<td>RBC transfusions by threshold blood Hb levels (90% capillary) and respiratory status Intubated: 113 g/l vs. 153 g/l Oxygen or continuous distending pressure: 93 g/l vs. 127 g/l  No respiratory support: 73 g/l vs. 67 g/l</td>
</tr>
<tr>
<td>Chen et al (2009)</td>
<td>Premature infants (birth weight &lt;1.5 kg)</td>
<td>RBC transfusions by threshold capillary blood Hct levels and respiratory status Intubated: 116 g/l vs. 150 g/l Continuous positive airway pressure: 100 g/l vs. 133 g/l  No respiratory support: 73 g/l vs. 100 g/l</td>
</tr>
<tr>
<td>Mukhopadhyay et al (2004)</td>
<td>Preterm infants (birth weight 1–1.8 kg)</td>
<td>RBC transfusion at Hb levels of ≤100 g/l vs. ≤ 133 g/l</td>
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<tr>
<td>Ransome et al (1989)</td>
<td>Preterm infants with GA at birth &lt;34 weeks and clinically well</td>
<td>RBC transfusions at Hb levels of 70 g/l or clinically symptomatic vs. Hb levels of 100 g/l</td>
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<tr>
<td>Brooks et al (1999)</td>
<td>All infants with birth weight &lt;1.251 kg at day 29 of life</td>
<td>RBC transfusions at Hb levels of 133 g/l versus clinically symptomatic</td>
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</table>

All pairs of Hb thresholds given are restrictive versus liberal. Hb, Haemoglobin concentration [for trials reporting haematocrit (Hct), conversion ×30 has been applied to the figures]; GA, gestational age; RBC, Red blood cell; IVH, intraventricular haemorrhage; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis. For further detail on trials see Venkatesh et al (2102).
separation achieved by the trial reported by Bell et al (2005), possibly due to increased transfusion for clinical need possibly due to the lower birth weight [mean birth weight: PINT Study 769 g (liberal) vs. 771 g (restrictive); Bell Study 954 g (liberal) vs. 958 (restrictive)]. Infants were also of lower gestational age in the PINT study compared to the Bell study [mean gestational age: PINT Study, 26-1 weeks (restrictive) vs. 26-1 (liberal); Bell Study, 27-7 (restrictive) vs. 27-8 (liberal)]. It should be noted that the use of restrictive thresholds in PINT resulted in modest reductions in exposure to transfusion.

The PINT study did not show any difference in terms of composite primary outcome of mortality, chronic lung disease, ROP, or brain injury (Kirpalani et al, 2006). Further neurodevelopmental follow-up did not show any difference between the two groups but a post hoc analysis favoured the liberal threshold arm in terms of a statistically significant difference in cognitive function between the infants treated at the low threshold [mean: 85.2; standard deviation (SD): 18.6; n = 156] compared with the high threshold (mean: 88.7; SD: 18.7; n = 164; Whyte et al, 2009). This difference, after adjustment for centre and birth weight stratum via multiple regression, of 4.3 points (95% CI: 0.4-8.2; P = 0.030) favoured the high threshold group by 0.29 SDs (Whyte et al, 2009). This result appears contrary to the follow-up study of the cohort reported by Bell et al (2005), which reported that neurocognitive and imaging indicators favoured the restrictive group over the liberal group (McCoy et al, 2011; Nopoulos et al, 2011). Unfortunately, no other study has evaluated neurodevelopmental follow up, although a trial in Germany has just started to recruit (Effects of Transfusion Thresholds on Neurocognitive Outcome of extremely low birth-weight infants, ETTCNO Study Group, 2012).

So, what are the implications of the results of these trials for Hb threshold-based current red cell transfusion practice in the UK? The core issue is the uncertainty surrounding neurological outcomes at more restrictive Hb thresholds. As indicated in a recent Cochrane review (Whyte & Kirpalani, 2011), local agreed thresholds for red cell transfusion should apply within the thresholds used in the liberal and restrictive arms across the trials described above, particularly the recent trials by Bell et al (2005) and the PINT investigators (Kirpalani et al, 2006). Safety at Hb thresholds below these levels has not been evaluated, and there appears no justification for applying higher levels. As a pragmatic summary based on the restrictive transfusion thresholds from the trials (Whyte & Kirpalani, 2011), outside the need for red cell transfusion to manage acute bleeding, additive small volume red cell transfusions might be considered when the Hb is <115 g/l for neonates requiring mechanical ventilation support, with lower thresholds applied for oxygen-dependent neonates not requiring ventilation or for late anaemia (Hb < 75–100 g/l, depending on gestational and post-natal age).

Recommendations of the British Committee for Standards in Haematology (BCH; Gibson et al, 2004) have been published, although it should be noted that these guidelines were formulated before the reports of the two RCTs described above. Later guidance has been published in the Handbook of Transfusion Medicine (McClelland, 2007). We also have an understanding of neonatal transfusion practice from the recent National Comparative Audit of the use of red cells in neonate and children (National Comparative Audit of Blood Transfusion, 2010), which indicates that neonatologists in the UK are using Hb triggers generally within the parameters recommended by the BCH guidelines but further stratified on the basis of postnatal age and respiratory status, and generally following a more restrictive pattern of usage. Table II provides suggested thresholds based on the practice of some of the authors reflecting consideration of all of the above sources. These thresholds may be used as an example for developing local guidelines pending the publication of updated recommendations from the BCH. Clearly, future red cell transfusion research must evaluate both short and long term neonatal outcomes including neurodevelopmental outcomes. There is also very little evidence to inform optimal target Hb post-transfusion.

What are component specifications for red cell transfusion?

Additional microbiological safety measures always apply for blood components for neonates in UK. These include the use of repeat donors (at least one donation in the last 2 years) and CMV negative donors. The Hct for red cell components for exchange transfusion and intra-uterine transfusion is tightly specified, whereas a broader range of Hct is acceptable for routine top-up transfusions. Exact specifications for neonatal components vary depending on different national blood transfusion services policies (New et al, 2009). After processing, components are screened for clinically significant blood group antibodies, and for high-titre anti-A and anti-B. In neonatal practice, because most red cell packs are stored in additive solutions for preservation, the amount of plasma ultimately transfused is very small, so any risks of haemolysis for a transfusion of Group O red cells with high-titre anti-A and anti-B that could cause lysis of A and/or B cells would be very low.

Historically, the recognition that addition of purine nucleosides to standard anticoagulant solutions significantly improved the viability of red cells led to the extensive use and development of different additive solutions, which allowed the shelf-life of red cell components to be extended prior to transfusion. Issues have been raised, however, about the safety of these solutions in transfused neonates. In the UK, the main optimal additive plasma replacement solution contains saline, adenine, glucose and mannitol (SAGM), which permits storage at 1–6°C for 35-d. The theoretical side-effects of adenine and mannitol in additive solutions for neonatal red cell transfusions include renal toxicity, particularly in the context of large volume red cell transfusions, such as...
compared RBC transfusions stored in different storage media. Some reassurance may be provided by four RCTs of the safety and effectiveness of different storage solutions. Specific to the UK, red cell units without additive solutions (i.e. in citrate phosphate dextrose anticoagulant) contain significantly greater volume of residual plasma in the transfused unit, which might increase the (theoretical) risk of variant Creutzfeldt–Jakob disease (vCJD) exposure.

Levels of evidence from RCTs for the safety and effectiveness of different storage solutions are limited in neonates. Trials that have been undertaken for small volume transfusions may provide some reassurance; for example, four RCTs compared RBC transfusions stored in different storage media (Goodstein et al, 1993; Liu et al, 1994; Strauss et al, 1996, 2000; Fernandes da Cunha et al, 2005), although results on clinical outcomes were variably described, including transfusion reactions (Strauss et al, 1996).

Given that red cell transfusions to infants contain smaller volumes, and in view of the desirability of reducing donor exposure, many countries, including the UK, split and reserve small volumes of red cells from a single donation for a neonate. An alternative approach to reduce donor exposure is to consider directed donations – red cell transfusions from individuals recruited by the families of neonates, who have donated blood specifically for their infant. One clinical trial (Lee et al, 1995) has specifically evaluated the use of a directed donor policy. This trial confirmed the potential for marked reduction in donor exposure in the study group, but there are potential challenges around directed donations, including counselling and testing in family members who are not regular blood donors. Regular blood donors form the safest group of donors, having being screened and tested for microbiological infections on multiple occasions. Regular donation also minimizes any risks associated with collection of blood that occurs during a ‘window’ period of infection.

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**Table II. A practical guide to transfusion of blood components in the neonate.**

<table>
<thead>
<tr>
<th>Type of blood component</th>
<th>Suggested indications for transfusion</th>
<th>Volume of transfusion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red cells</strong></td>
<td>Top-up transfusion thresholds are dependent on postnatal age and respiratory status of neonate</td>
<td>10–20 ml/kg</td>
<td>Higher end of dose range for severely anaemic or bleeding neonates</td>
</tr>
<tr>
<td>Age &lt;1 week: Hb &lt;120 g/l</td>
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<tr>
<td>Age &gt;1 week: Hb &lt;110 g/l</td>
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<tr>
<td>On Oxygen/nCPAP</td>
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<tr>
<td>Age &lt;1 week: Hb &lt;100 g/l</td>
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<td></td>
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<tr>
<td>Age &gt;1 week: Hb &lt;90 g/l</td>
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<tr>
<td>Stable and off oxygen support</td>
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<tr>
<td>More than a week: Hb ≤ 75 g/l</td>
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<tr>
<td><strong>Platelets</strong></td>
<td>Platelet count &lt;100 x 10⁹/l</td>
<td>10–20 ml/kg</td>
<td>Higher end of dose range should be considered for bleeding</td>
</tr>
<tr>
<td>Neonates with major bleeding or requiring major surgery (e.g. neurosurgery)</td>
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<tr>
<td>Platelet count &lt;50 x 10⁹/l</td>
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<tr>
<td>Neonates with bleeding, current coagulopathy, surgery or exchange transfusion, infants with NAIT if previously affected sibling with ICH</td>
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<tr>
<td>Platelet count &lt;20–30 x 10⁹/l</td>
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<tr>
<td>Neonates with no bleeding (including NAIT if no bleeding and no family history of ICH)</td>
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<tr>
<td><strong>FFP</strong></td>
<td>Infants with abnormal coagulation profile and active bleeding</td>
<td>10–20 ml/kg</td>
<td>Higher end of dose range if volume not critical and for bleeding</td>
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<tr>
<td>Infants with abnormal coagulation profile and undergoing surgery</td>
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<tr>
<td>Abnormal coagulation profile may be defined as PT or APTT &gt;1.5 times the mid-point of the gestational and postnatal age-related reference range, and should take into account any local laboratory ranges</td>
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FFP, fresh frozen plasma; Hb, haemoglobin concentration; PT, prothrombin time; APTT, activated partial thromboplastin time; NAIT, neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage; DIC, disseminated intravascular coagulation; NEC, necrotizing enterocolitis; HIE, hypoxic ischaemic encephalopathy; BCSH, British Committee for Standards in Haematology; NICU, neonatal intensive care unit.
Current BCSH guidelines (Gibson et al., 2004; Treleaven et al., 2010) recommend the use of irradiated blood in neonates with known or suspected congenital cell immunodeficiency, and those who have received intratracheal transfusions and exchange transfusion (if the time delay is acceptable). Irradiated blood may reduce the risk of rare complication of transfusion graft-versus-host disease. CMV is a cell-associated virus and ubiquitous in blood donors, with seropositivity rates ranging from 30% to 70%. Congenital CMV infection can cause serious disease in the fetus and neonate although exact risks of post-natally-acquired CMV disease and the benefits of screening strategies in the NICU are still unclear (Josephson et al., 2011). In the UK, universal leucodepletion of all blood components was introduced in 1999. Recent recommendations from Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO; the position statement, together with a more detailed report, are available at http://www.dh.gov.uk/health/2012/03/sabto/) considers leucodepletion as CMV-safe for most transfusion recipients, although they recommended that fetuses and neonates up to 28 d post-expected delivery date should continue to also receive CMV sero-negative components.

There remains uncertainty around the optimal age of stored red cells for neonatal transfusion, which may be clarified with the anticipated publication of the Age of Red Blood Cells in Premature Infants (ARPI) study (Fergusson et al., 2009). A number of observational studies have reported that, with increased storage time, red cells undergo different cellular and biochemical changes that, in turn, may affect tissue oxygenation and contribute to adverse outcomes including increased length of hospitalization, multiorgan failure, tissue oxygen delivery and mortality (Bunn et al., 1969; Strauss et al., 1996, 2000; Purdy et al., 1997; Walsh et al., 2004; Hebert et al., 2005; Koch et al., 2008; Edgren et al., 2010; Karam et al., 2010). In the neonatal literature, a number of smaller trials have evaluated the effects of transfusing older stored red cells (Liu et al., 1994; Lee et al., 1995; Strauss et al., 1996, 2000; Fernandes da Cunha et al., 2005) although only two trials (Lee et al., 1995; Fernandes da Cunha et al., 2005) reported on mortality and found no significant difference.

**Administration of red cell transfusions?**

Standard practice in hospitals is to transfuse group-specific red cells to all recipients. Due to the relative immaturity of the neonatal immune system, infants generally do not form allo-antibodies to red cell antigens in the first 4 months of life. Red cell antibodies in the peripheral blood are those transferred from the mother. Therefore the policy for hospital cross-matching prior to a first transfusion in neonates is to request samples from the mother for ABO, RhD grouping and antibody screening, which helps avoid taking volumes of blood from the infant for antibody screening, which are more equivalent to volumes routinely collected from adults. Neonatal red cells must be grouped for ABO and RhD. If no allo-antibodies are present in the maternal (or infant) sample, repeat compatibility testing is not required for the first 4 months of post-natal life. Red cells selected for transfusion are group-identical, or group compatible with both baby and any antibodies in maternal plasma. It is common blood bank practice for group O to be issued rather than ABO compatible with the neonate, in order to avoid the potential risk of haemolysis from maternal IgG anti-A or B where there is ABO incompatibility between mother and baby (and as Group O is the more common group of red cells with neonatal specifications provided by Blood Transfusion Services).

Neonates are usually administered red cell transfusion volumes of around 15 ml/kg in order to correct anaemia although greater volumes may be prescribed to treat bleeding. Prescribing in neonates and infants must be in millilitres and not ‘units’, as there have been reports of accidental or erroneous over-transfusion when prescribing by units. Red cells can be infused through small-bore needles although transfusion through needles of <27 G is probably not possible. Traditionally, small volume transfusions can be performed without the use of a blood warmer. Filtration using standard pore size filters (170–200 µm) is usually performed to remove aggregates, and small-volume neonatal infusion sets will reduce the prime volume.

It should be acknowledged that evidence for safe administration rates is very limited. Only one trial (Nose et al., 1996) has evaluated different rates of transfusion (transfusion over 3 h versus transfusion over 12 h), and found no differences in the outcomes of necrotizing enterocolitis (NEC) and nosocomial infections. However the trial did find a significant increase in ejection fraction during transfusion in the rapid transfusion group. Two trials have evaluated different transfusion volumes (10 ml vs. 20 ml/kg; Wong et al., 2005; Gupta et al., 2007). The outcomes reported by the trials varied, with one study reporting on mesenteric blood flow (Gupta et al., 2007) and the other on mortality (Wong et al., 2005) but neither trial found significant differences in outcome based on transfusion volume.

Neonates receiving red cell transfusions must have a unique patient identification number, such as hospital number, National Health Service (NHS) number or emergency admission number. Experience in many countries, including the UK, has indicated that morbidity and mortality is associated with errors in the processing and administration of blood, often involving errors in correct patient identification. Locally agreed hospital policies for patient identification and safe administration must apply to the unique setting of neonatal units, with the challenges of multiple births and the same surname.

**What are the risks of red cell transfusion?**

Interpretation of the data from the UK Serious Hazards of Transfusion (SHOT) National Haemovigilance Scheme against a population based epidemiological study of transfused
patients has suggested that a disproportionate number of all adverse events occur in children compared to adults, and more so in infants and neonates (Stainsby et al., 2008). A significant proportion of these reports were related to transfusion errors, including transfusion of an incorrect blood component. In this report, based on data over a 9-year period, there was one case of transfusion-associated graft-versus-host disease (from non-irradiated red cells) reported in a 13-d-old infant born at 32 weeks gestation. There were no reported cases of transfusion-transmitted infection in neonates. In the most recent 2011 annual SHOT report (Bolton-Maggs & Cohen, 2012), there were also no paediatric cases of transfusion-transmitted infection. Whilst these low numbers are reassuring – a testament to the on-going rigour of donor selection criteria and high standards of collection, processing and testing – there always remains the risk of new pathogens entering the transfusion chain. To date there have been four cases of vCJD prion transmission through red cells transfusion (from 3 donors) and concerns about possible transfusion-transmitted vCJD are highly relevant for neonatal transfusion practice, given the long life expectancy of many of these recipients. The numbers of suspected and proven viral transfusion-transmitted infections remain much smaller than for bacterial transfusion-transmitted infections. The risk of bacterial transfusion-transmitted infection in the UK was highlighted via a national transfusion alert from the Royal College of Paediatrics and Child Health and National Health Service Blood and Transplant, following an episode of bacterial contamination of platelet concentrates in an infant (www.rcpch.ac.uk).

While SHOT has received numerous reports related to transfusion errors in the neonatal age group, there have been relatively fewer adverse reactions to transfusion reported. In the 2011 Annual SHOT Report (Bolton-Maggs & Cohen, 2012), there were no reports of transfusion-related lung injury (TRALI) in neonates or infants. There were five paediatric reports classified as transfusion-associated circulatory overload (TACO) including in neonates. It seems likely that there is under-recognition and/or underreporting of adverse events in infants due to pre-existing critical illness and probably also difficulties defining these events in a neonatal setting.

Of note, in the 2011 Annual SHOT Report, there were two cases of NEC possibly associated with red cell transfusion in 5- to 6-week-old preterm infants, one of whom subsequently died. NEC has a mean prevalence of 10-2% in infants with birth weights of <1.5 kg, with mortality between 20% and 30% (Uauy et al., 1991; Lemons et al., 2001). An association between transfusion and NEC was first suggested in 1987 during an outbreak of NEC in a neonatal unit in Oklahoma, with a significant association between transfusion and NEC with an odds ratio of 15:1 (95% CI, 2.6–92:5; McGrady et al., 1987). Christensen et al. (2010) compared the use of transfusion in cases of NEC and surgical intervention to matched controls. The authors did not report an excess of blood transfusion in cases of NEC; however, a greater proportion developed NEC within 48 h of a blood transfusion compared to those cases of NEC without an antecedent transfusion. Other studies have raised the issue of relationship to antecedent transfusion (Josephson et al., 2010; Paul et al., 2011), although there are major limitations to the strength of any conclusions possible from retrospective studies. A recent systematic review of the wider literature addressing the association between transfusion and NEC also suggested that recent exposure to transfusion was associated with NEC in neonates, and that neonates who developed transfusion-associated NEC were at higher risk of mortality, but clearly there are many confounding factors affecting the strength of conclusions (Mohamed & Shah, 2012). Further work also needs to consider relevant mechanisms (Reynolds et al., 2007; Kim-Shapiro et al., 2011). Blau et al. (2011) have suggested that an association may represent immune-mediated gut injury not dissimilar to TRALI. At present, without prospective studies, it seems difficult to advocate changes in neonatal feeding policies, although one study has reported a reduction in the incidence of NEC when withholding feeds during a transfusion (El-Dib et al., 2011).

A main clinical concern in neonatal practice is intracranial haemorrhage, specifically intraventricular and periventricular haemorrhage (IVH–PVH). The incidence of major IVH–PVH may exceed 30% in the most premature neonates, and around three-quarters of IVH–PVH develop in the first 48 h after birth. Because the premature neonatal brain is relatively fragile, with a poorly developed subependymal matrix and weak endothelial supporting structures, it is not surprising that rupture of small blood vessels for any reason is a real risk. Relevant factors in the aetiology of IVH–PVH include cardiovascular and respiratory instability and changes in vascular perfusion pressures, both perinatally and postnatally (de Vries, 2012). Perhaps not surprisingly, these mechanisms may also apply when considering possible associations reported between red cell transfusion itself and occurrence of IVH (Baer et al., 2011a). This association serves as an example of additional risks that may be poorly captured in current haemovigilance schemes (Rao et al., 2004). It is possible that red cell transfusions may cause haemodynamic compromise by impairing cardiac function, as routine transfusion volumes on the basis of ml/kg body weight may be higher in neonates when compared to adults. Echocardiographic abnormalities in anaemic infants may persist for greater length of time following a transfusion (Alkalay et al., 2003). Haemovigilance schemes also do not capture the problems of maintaining vascular access in small infants with risks of extravasated/infected intravenous cannulae. Finally, any transfusion of red cells is ‘contaminated’ with a small numbers of lymphocytes, although the exact clinical consequences of all immunomodulatory effects, such as increased rates of infection, remain unclear (Vamvakas & Blajchman, 2009).
Summary recommendations for red cell transfusion

In conclusion, the above series of questions serves as a framework for considering the balance of benefits versus risks when deciding to transfuse red cells to neonates. Most red cell transfusions will be considered in the context of small-volume transfusions. Given uncertainties surrounding evidence of effectiveness, it seems prudent to follow a generally restrictive policy, within the limits described earlier in the trials and as summarized in Table II. Locally agreed guidelines for blood testing and safe blood transfusion are also key to minimizing unnecessary transfusions and reducing risks in neonates. Locally agreed guidelines for red cell transfusions should also be supported by strategies for effective implementation (Motta et al, 2010; Baer et al, 2011b).

Use of platelets and plasma for transfusion

The same series of questions, as described above for red cell transfusion, should be considered when deciding whether a neonate needs a platelet or plasma transfusion (Table II). As a generalization, levels of evidence underpinning recommendations on safety and effectiveness of platelet and plasma transfusion to neonates are far less clear than for red cells. Space does not permit wider consideration of all points, and the reader is also referred to a recent review on platelet transfusions (Chakravorty & Roberts, 2012).

The only readily available specific treatment for thrombocytopenia in neonates is platelet transfusions. Two types of platelet products are available: pooled platelets derived from whole blood donations from donors, and apheresis platelets collected by cell separation techniques from donors. In the UK, splits of units of platelet concentrates will be prepared from apheresis collections for neonatal use, selected according to neonatal specifications. While the use of platelet transfusions for neonates with thrombocytopenia and active bleeding is not questioned, there remains considerable uncertainty in their wider use as prophylaxis for neonates who are clinically stable and not actively bleeding. Several surveys of neonatologists have shown markedly different practices in the use of platelet transfusions. In the only randomized controlled trial in neonates to assess a threshold level for the effectiveness of prophylactic platelet transfusions, moderate thrombocytopenia (defined as 50–150 × 10^9/l) was not detrimental to short-term neonatal outcome, specifically to prevent risk of progression of IVH–PVH (Andrew et al, 1993). A multicentre prospective observational study of 169 neonates with platelet counts of <60 × 10^9/l has shown that 69% of neonates received platelet transfusions, with the 50th and 90th centile of pre-transfusion platelet counts being 27 and 48 × 10^9/l, and the majority of transfusions were prophylactic (Stanworth et al, 2009). There was no evidence of a relationship between platelet count and occurrence of major haemorrhage (Muthukumar et al, 2012).

Practice in some neonatal units in the UK has now seen levels of platelet count thresholds for prophylactic transfusions fall to 20–30 × 10^9/l in stable neonates (Stanworth et al, 2009), although many neonatologists might consider higher thresholds in unstable premature neonates in the first week of life. Although there is no high quality evidence base to support the safety of prophylactic thresholds at any level below 50 × 10^9/l in neonates, a number of clinical studies are starting to address the safety of lower thresholds, including a randomized controlled trial (http://www.planet-2.com). Such trials will need to be of a large sample size for clinical outcomes, given the heterogeneity of causes of thrombocytopenia. As for all blood components, if the safety of lower transfusion thresholds is established, one would anticipate cost-savings.

Fresh frozen plasma (FFP) is not infrequently transfused to neonates. FFP is human donor plasma either recovered from a single whole blood donation or obtained by plasmapheresis and frozen within a specific time period after collection. After thawing, although diluted with citrate anticoagulant, FFP contains near normal levels of many plasma proteins, including procoagulant and inhibitory components of the coagulation cascades, acute phase proteins, immunoglobulins and albumin. In the UK, plasma for neonates is imported and pathogen inactivated. Several clinical scenarios for FFP transfusion apply and are repeatedly identified in audits, including treatment of bleeding in association with laboratory evidence of coagulopathy, correction of disseminated intravascular coagulation (DIC), prevention of intraventricular haemorrhage, management of very sick unstable infants (e.g. during sepsis or as a volume expander) or correction of markers of prolonged coagulation in the absence of bleeding. The findings of a national comparative audit of transfusion practice have indicated almost half of FFP transfusions are given to babies with abnormal coagulation values with no evidence of active bleeding (Stanworth et al, 2011). Much of the uncertainty around transfusion of FFP stems from the unique development of the neonatal coagulation system, and a lack of appreciation of reference ranges to define neonatal coagulopathy; of note, the most widely quoted reference range in preterm babies did not evaluate the coagulation profile of babies <30 weeks gestation (Andrew et al, 1987, 1988).

It is also widely accepted that standard coagulation tests have significant limitations as predictors of bleeding in any patient group, including neonates, and that the use of FFP also has little effect on correcting abnormal coagulation tests when mild and moderate results are recorded (Segal & Dzik, 2005; Callum & Dzik, 2010). Overall, there is no support for evidence of effectiveness for the prophylactic use of FFP when reviewing the wider neonatal randomized controlled trial literature or those trials evaluating use of plasma to prevent intraventricular haemorrhage (Northern Neonatal Nursing Initiative Trial Group, 1996; Stanworth, 2007; Yang et al, 2012).
Fresh frozen plasma transfusions to neonates should be considered in the clinical context of bleeding (e.g. vitamin K-dependent), DIC, and very rare inherited deficiencies of coagulation factors. There seems no role for prophylactic FFP to prevent intraventricular haemorrhage or for use as a plasma expander. Abnormalities of standard coagulation tests should not be interpreted in isolation, but alongside reference ranges for gestational age and post-natal age as well as review of bleeding history and other haemostatic markers, such as platelet count. In practice, an appropriate plasma transfusion strategy in neonates should be one that emphasizes the therapeutic use in the face of bleeding, rather than prophylactic use in association with abnormalities of standard coagulation tests, which have very limited predictive value for bleeding (Segal & Dzik, 2005).

**Conclusion**

Recent trials of red cells have provided an initial evidence base in this high-risk population. However, we still lack definitive answers to basic transfusion questions and the risk benefit ratio for transfusion in neonates remains unclear. Further RCTs of red cell transfusion (adequately powered to assess long term neurodevelopmental outcomes) are necessary to address uncertainties in restrictive transfusion practice. Nonetheless, there seems no reason to recommend policies for transfusion of red cells, platelets and plasma that do not advocate restrictive use of components.

**Authors’ contributions**

All authors contributed to the writing of this paper.

**Financial disclosure**

The authors have no financial relationships relevant to this article to disclose.

**Conflict of interest**

The authors have no conflict of interest relevant to this article to disclose.

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Review


