Vox Sanguinis (2006) **90**, 1–9

REVIEW

Paediatric transfusion

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Vox Sanguinis

Received: 22 April 2005, revised 4 October 2005, accepted 4 October 2005

The requirements of children undergoing transfusion should be considered as a distinct entity from those of adults. Neonates are particularly vulnerable and there have been concerns over infective or toxic risks to this group. Neonates may also have more acute side-effects as a result of their small blood volume. Most children who are transfused will have a good life expectancy, so long-term side-effects will be more significant than for adults. In Britain, there are a number of transfusion components with neonatal specifications, but there appears to be some confusion, among both medical and laboratory staff, as to the appropriate use of these. Although there are many paediatric guidelines on the use of blood, there is a lack of evidence underlying these. However, there are trends to decreased blood usage in neonates and ongoing studies to investigate the appropriate use of blood for children.

Key words: neonatal transfusion, paediatric components, transfusion toxicity.

Introduction

Although the field of transfusion medicine for children shares many of the same principles as that for adults, it also has distinctive elements which need to be considered separately. Children are a vulnerable group with special requirements, and those who require blood transfusion are among the most intensively transfused patients. They are likely to have a long life span post-transfusion, so minimizing adverse consequences will lead to significant benefits. As a result of the small overall numbers transfused, relative to adults, the specialist needs of children may be overlooked.

Paediatric transfusion has two major themes: the best product to use, and suitable transfusion triggers to ensure the appropriate use of blood. In addition, it is important to consider alternatives to transfusion and ways of reducing the need to transfuse. In this review the main reasons for considering children as a separate population, and the constraints that this places on the component specification for them, will be highlighted. The evidence and guidelines available as to the appropriate way in which to transfuse children with these products will also be outlined.

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Why are there particular concerns with paediatric transfusion?

Vulnerable recipients

Neonates, particularly those who are preterm, are especially vulnerable to the potential infective and toxic effects of transfusion. They have immature immune and metabolic processes, and are still undergoing rapid neurodevelopment. Cytomegalovirus (CMV) infection may be transfusion transmitted, and is a particular risk for causing severe disease in low-birthweight babies (< 1500 g) [1]. The risk of CMV infection is reduced by leucodepletion or by the use of blood from CMV-seronegative donors [2].

The immaturity of the fetal and neonatal immune system leads to concerns regarding the risk of transfusion-associated graft vs. host disease (TA-GVHD). Most of the reported cases of TA-GVHD in neonates with normal immunity have occurred following intrauterine transfusions (IUT) or exchange transfusions (particularly when following IUT), with only rare cases of TA-GVHD being reported following simple transfusions to preterm neonates [3]. TA-GVHD has also been described in infants with primary cellular immunodeficiency disorders, and it may be difficult to recognize these early in life. For example, TA-GVHD has been reported following neonatal cardiac surgery where the diagnosis of DiGeorge syndrome (cardiac anomalies, congenital immunodeficiency and chromosome 22q11 microdeletions) had been missed [4].

Table 1 Summary of some of the preservative solution constituents present in units of packed red cells[a]

	AS-1 (Adsol)	AS-3 (Nutricel)	AS-5 (Optisol)	SAG-M	Predicted toxic dose
Volume (ml)	100	100	100	100	
Sodium chloride (mg)	900	410	877	877	137 mg/kg/day
Dextrose (mg)	2200	1100	900	–	240 mg/kg/h
Glucose (mg)	–	–	–	818	–
Adenine (mg)	27	30	30	16·9	15 mg/kg/dose
Mannitol (mg)	750	–	525	525	360 mg/kg/day
Trisodium citrate (mg)	–	588	–	–	180 mg/kg/h
Citric acid (mg)	–	42	–	–	–
Sodium phosphate (monobasic) (mg)	–	276	–	–	> 60 mg/kg/day

[a]This table is a modification of previously published data [5,65].

There are concerns over the potential toxic effects to neonates of some additives [in particular adenine (renal toxicity) and mannitol (renal and neurotoxicity)] in red cell preservative solutions [5]. All substantial evidence in the literature relating to this has been either theoretical or relates to small-volume neonatal top-up transfusions. The main theoretical evidence is from Luban and colleagues [5], who estimated the quantities of red cell additives that would be transfused to neonates given red cells suspended in Adsol (see Table 1 for constituents) in small-volume transfusions or in large-volume transfusions, such as exchange transfusion or cardiac bypass/extracorporeal membrane oxygenation (ECMO). They calculated that small-volume transfusion of red cells in extended-storage media should not result in toxic levels of additives in the recipients. However, in massive transfusion settings, such as ECMO, the estimated levels of transfused additives did appear to approach toxicity. Data on the actual pharmacodynamics and toxicities of the additives in these settings were unavailable so it was impossible to be sure of the actual level of risk, but the authors advised avoiding exposure of neonates to large quantities of these additives.

Subsequent studies *in vivo* have confirmed the safety of additive solutions in neonatal small-volume transfusions [3,6]. However, until recently there has been no clear evidence in the literature as to the actual risks in large-volume transfusions, and therefore practice has continued on the basis of the theoretical concerns, with a large body of opinion in favour of caution. For example, in Canada, additive solutions are often removed before large-volume transfusions are undertaken [7]. Nonetheless, it is important to note that several of the major paediatric cardiology centres in the UK routinely use SAG-M blood for large-volume transfusions (see Table 1 for constituents), and that mannitol is frequently used in cardiopulmonary bypass priming solutions [8,9].

Recently, results of a prospective randomized trial have been published, comparing transfusion of whole blood with reconstituted blood for 200 infants undergoing cardiac surgery [9]. The reconstituted blood was made up of packed cells in Adsol or Optisol combined with fresh-frozen plasma (FFP), and therefore contained adenine and mannitol (see Table 1). The group that received reconstituted blood had a better outcome (a shorter stay in intensive care and decreased perioperative fluid overload) than the group that received fresh whole blood. Moreover, there was no significant difference in the number requiring renal replacement therapy. This study therefore provides evidence of the apparent safety of mannitol and adenine in neonatal cardiac surgery and it may be possible to use these additives more widely in this situation in the future. However, it is not clear as to how much adenine and mannitol (both small molecules) may be removed during the haemofiltration processes that frequently take place during paediatric cardiac surgery [9,10], so it is difficult to extrapolate from this setting to others, such as neonatal exchange transfusion.

Other concerns regarding toxicities of transfusion to neonates include the effects of lead. In children, a greater proportion of circulating lead reaches the brain, and the developing nervous system is especially vulnerable to damage [11]. Bearer and colleagues [12] showed that some red cell units transfused to neonates in California had lead concentrations that were sufficient to cause unacceptably high post-transfusion blood lead levels. This could be a particular problem if a unit of blood with an excessive lead level were a designated 'paedipack' for a particular neonate. They recommended that all units for paediatric patients should be screened for lead concentration [13].

Acute side-effects

The acute side-effects of transfusion may be greater for small children than for adults, as a single unit of transfused blood with the potential to cause harm may represent a much greater proportion of their blood volume than that in an adult. For example, towards the end of their shelf-life, or after storage postirradiation, red cell units have potassium levels that are high enough to cause significant hyperkalaemia if they are

rapidly transfused to a small child. There have been reports of this causing cardiac arrest and death [14,15]. Similarly, there are concerns over the effect of iso/alloantibodies, and where large volumes of plasma or platelets from group O donors are transfused into children who are not group O there may be significant haemolysis as a result of anti-A,B [16,17].

Long-term side-effects

The majority of children will survive the event for which transfusion is required, and most will live for several decades afterwards. This contrasts with the outcome for the transfused population as a whole, where one study has shown a median survival of 51 months [18]. Consideration of long-term side-effects for children is therefore particularly important.

Infections with a long incubation period

Infections of particular potential long-term significance for the paediatric population include the human T-cell leukaemia viruses (HTLV) and variant Creutzfeldt–Jacob disease (vCJD). HTLV-I infection may cause chronic neurological disorders or adult T-cell leukaemia/lymphoma, decades after transfusion [19]. The HTLV seropositivity rate of European blood donors is between 0·001% and 0·03% [20]. In the UK, universal leucodepletion since 1999 will have reduced the levels of HTLV-I and -II [21], and screening for HTLV-I and -II was subsequently introduced in 2002. Therefore, HTLV-I and -II infection should not now be transmitted by transfusion, but small numbers of older children may be incubating the disease from earlier transfusion episodes.

The avoidance of potential transfusion transmission of vCJD is a current concern in the UK, and is having a major impact on the source and processing of blood products, particularly for children. vCJD is a transmissible encephalopathy that is almost certainly caused by infection of humans with bovine spongiform encephalopathy (BSE) prions [22]. There have been 155 definite or probable cases in the UK to date [23], mostly in young people. The epidemic appears to have peaked, but this is not certain and it is also not clear how many asymptomatic people may be carrying the disease [24].

In 2004 there were two reports of possible transfusion transmission of vCJD in the UK; both were from donors who were asymptomatic at the time of donation but later died of vCJD [25,26]. A number of measures have been introduced to try to reduce the possible transfusion transmission of vCJD in the UK, including universal leucodepletion and exclusion from donation of previously transfused individuals, the rejection of all UK plasma for fractionation and the importation of plasma from the USA for this purpose. Leucodepletion does not remove all infectivity [27], and it is thought, by some, that the majority of residual infectivity is plasma-associated. Other recent measures have therefore been taken to reduce the exposure of young children to UK plasma (see below).

Iron overload

Patients on chronic transfusion programmes, for conditions such as β-thalassaemia major or myelodysplasia, will develop iron overload [28]. However, serious sequelae as a result of this, such as liver cirrhosis, cardiac problems, or endocrine impairment, may not occur for several years [29]. As a result, it may be reasonable to delay iron chelation in an elderly adult patient, whereas children require meticulous treatment with desferrioxamine as soon as they are old enough to tolerate the drug [28] while at the same time being transfused to a high enough level to permit normal growth and development.

Alloimmunization

Neonates who are transfused do not tend to make alloantibodies in the first few months of life [30]. However, alloimmunization of older children may occur, and this is an issue, particularly for females in the case of future pregnancy. A recent study of pregnant women with anti-Kell showed that 82·1% had Kell-negative partners and that more than half of those women were known to have been previously transfused. This suggests that transfusion is a significant cause of Kell alloimunization [31]. The same was not true for women with anti-c, where 96·7% had a c-positive partner. RhD-negative blood is routinely given to Rh-negative female children and women of childbearing age, and it may also be beneficial to give Kell-negative blood to females in this age group in order to reduce the future occurrence of haemolytic disease of the newborn in their offspring.

Patients with sickle cell disease are particularly vulnerable to alloimmunization, with the rate increasing with increasing number of transfusions [32]. If a child becomes alloimmunized, they have many years ahead in which they may need further transfusions, and they may subsequently develop sufficient additional antibodies to cause difficulties in the provision of blood for transfusion. It has been shown that phenotype matching for Cc, Ee and Kell reduces alloimmunization and haemolytic transfusion reactions in children with sickle cell disease when compared with studies of patients given standard matched red cells [33], and it is therefore widely recommended that all children with sickle cell disease are given fully Rh-matched and Kell negative blood [34].

The impact of these issues on the products available in the UK

There are a number of components designed specifically for paediatric use, most being for neonates. Some of the general principles are discussed below, and details are available in the British Committee for Standards in Haematology (BCSH) guidelines [34]. In order to minimize the risk of infection,

products for neonates are from CMV-negative 'accredited' donors who have donated at least once within the previous 2 years. Donor exposure is reduced by using designated 'paedipacks', where multiple neonatal small-volume transfusions can be given from the same donation up to the expiry date [35]. Despite these measures, neonates requiring transfusion during surgery are sometimes given standard adult red cells; this is not desirable and should be avoided if possible. For older children on long-term transfusions, such as those with thalassaemia, donor exposure may be reduced by using 'double dose' red cells obtained by apheresis [36].

The risks of vCJD for children are minimized, as far as possible, by importing FFP from the USA for those born after January 1996 (and therefore assumed not to have been exposed to BSE in the food chain), although cryoprecipitate is currently sourced from the UK. The provision of US FFP will be extended for all children in the near future. It appears that the main residual exposure of young children in the UK to UK plasma is from blood without additive solutions, but containing significant residual plasma, used predominantly for neonatal exchange transfusions and by some paediatric cardiac surgery centres. Red cells suspended in SAG-M additive solution have little plasma, so it may be possible to reduce still further the risk of vCJD by using this product more widely in neonatal cardiac surgery (see above).

TA-GVHD is prevented by the irradiation of cellular blood products destined for use in high-risk situations, including IUT, exchange transfusion following IUT, recognized congenital cellular immunodeficiency and stem cell transplantation [37]. However, situations such as exchange transfusion alone or simple neonatal prematurity are more uncertain, and the benefits of widening irradiation indications have to be balanced against the risk of increased potassium levels if blood is stored postirradiation and of significant delays in blood availability if irradiation is performed off-site. These uncertainties have led to variations in guidelines between countries such as the UK and the USA [38], and also to variations in practice between centres within the USA [3]. It is difficult to overcome concerns over missing congenital immunodeficiency in the early months of life without irradiating all blood for these infants and thereby introducing other risks. However, alternative ways of addressing this problem in specific situations include the introduction of preoperative immunological screening of infants undergoing cardiac surgery in order not to miss DiGeorge syndrome [4].

To reduce problems with hyperkalaemia following large-volume transfusion, blood for exchange transfusion and cardiac surgery in neonates is less than 5 days old, and used within 24 h if irradiated, unless subject to washing procedures [34]. The red cell haematocrit is between 0·5 and 0·7 for standard paediatric and neonatal top-up transfusions, but this is adjusted for certain other indications. For IUTs, a higher haematocrit is used in order to minimize the number of procedures needed by maximizing the red cell volume transfused. For neonatal exchange transfusions, there is a lack of consensus over the optimal product and haematocrit, with some neonatologists preferring to use whole blood [39,40]. The BCSH guidelines [34] recommend the use of red cells with a more tightly regulated haematocrit, 0·5–0·6, in order to generate an acceptable postexchange haemoglobin (Hb) level.

Finally, to reduce the potential for neonatal morbidity from donor antibodies, all blood for neonates undergoes screening for high-titre anti-A and anti-B, and for atypical antibodies. It is recommended that group O FFP and platelets if possible, should not be used for neonates or infants who are not group O [34,41], particularly following reports of morbidity in children following the usage of group O plasma for non-group O neonates and children [16,17].

Confusion over the correct blood product – not an idle worry

The choice of component for transfusion to neonates is not straightforward, and there are frequent instances where the appropriate product is not chosen. These have been highlighted in the most recent report of the UK haemovigilance scheme, Serious Hazards of Transfusion (SHOT) [17]. Fifty-nine of 449 (13%) analysable reports were on children less than 18 years of age, many of whom were in their first month of life. The majority of incidents involved transfusion of an incorrect blood component (IBCT), often as a result of the failure to request or issue components of the correct specification. The problems were various, but included failure to irradiate or to give CMV-negative components. Overall, 8% of IBCT incidents were to children less than 12 months old, and as it is estimated that only ≈ 1·2% of red cells are transfused to this population [42], this suggests a disproportionate number of errors in this group.

One of the reasons for these errors may be a lack of knowledge of the special requirements for paediatric transfusion. Transfusion of children occurs mainly in specialist situations, such as neonatal and paediatric intensive care, cardiac surgery/ECMO, and haematology–oncology/bone marrow transplantation. As other paediatric populations are rarely transfused, this leads to a lack of expertise among junior staff rotating between specialties. In addition, there are practical bedside issues for neonates, such as the difficulty in finding room for wristbands on tiny preterm babies, fraught clinical situations and complex administration issues.

Appropriate use of paediatric transfusion

Neonates

There are many paediatric transfusion guidelines, which are largely based on consensus opinion as there is little evidence

Table 2 Suggested transfusion thresholds for neonates[a]

	Transfusion threshold
Transfusion of red blood cells	
Anaemia in the first 24 h	Hb < 12 g/dl
Neonate receiving mechanical ventilation	Hb < 12 g/dl
Acute blood loss	≥ 10% blood volume lost
Oxygen dependency (not ventilated)	Hb < 8–11 g/dl (depending on clinical situation)
Late anaemia, stable patient (off oxygen)	Hb < 7 g/dl
Transfusion of platelets	
Consider in all neonates	$< 30 \times 10^9$/l
Consider if increased bleeding risk, for example:	$< 50 \times 10^9$/l
• < 1000 g and < 1 week of age	
• clinically unstable (e.g. labile blood pressure)	
• previous major bleeding (e.g. grade 3–4 intraventricular haemorrhage)	
• current minor bleeding (e.g. petechiae)	
• coagulopathy	
• planned surgery or exchange transfusion	
Major bleeding	$< 100 \times 10^9$/l

[a]This table is adapted from previously published data [34,44], and may serve as a starting point for developing local guidelines.

from controlled studies [34,38; see also 43]. Transfusion triggers are one of the main areas of uncertainty, and it is particularly difficult to extrapolate adult data to neonates. Neonatal red cell transfusions are mostly given to preterm babies to replace blood taken for testing, and the transfusion trigger will vary depending on a number of parameters, including neonatal age and cardiorespiratory status. This has been recently reviewed by Murray & Roberts [44], and there is a trend to gradually reduce the red cell transfusion triggers in this setting without evidence of increased morbidity (see also Table 2). A randomized study has recently been reported (the premature in need of transfusion, 'PINT' study) [45] where extremely low birthweight (< 1000 g) neonates were divided into two groups, namely those who received transfusions at a lower or a higher Hb threshold. This resulted in a difference in mean Hb of ≈ 10 g/l between the groups, and although there was no significant difference in the mean number of transfusions, those at the lower threshold were more likely to have no transfusion at all (13% vs. 6·1%). There was no obvious detrimental effect of the lower threshold when a composite outcome, measuring morbidity and mortality, was used.

Accepted indications for FFP use on neonatal units have also become more restricted. For example, its use as volume replacement, or for the treatment of sepsis, is no longer considered appropriate [34,44]. Current guidelines recommend FFP primarily for bleeding as a result of vitamin K deficiency, for bleeding or significant bleeding risk owing to coagulopathies such as disseminated intravascular coagulation, and for the treatment of inherited single-factor deficiencies where there is no concentrate available [34,41]. However, there is little evidence from randomized controlled trials regarding the use of FFP in neonates [46], and little data on outcome. In particular, there are ongoing uncertainties as to the role of prophylactic transfusion to prevent peri-ventricular haemorrhage (PVH) in preterm neonates. A large prospective randomized controlled trial by the Northern Neonatal Nursing Group [47,48] showed no benefit of prophylactic FFP or albumin given to preterm babies to prevent PVH, and as a result it is not recommended to give FFP as routine prophylaxis for this indication [41]. However, the study did not include measurement of coagulation, and it is possible that a subset of preterm babies with a coagulopathy might benefit from prophylaxis in this situation.

Platelet transfusions are given to a substantial number of babies in neonatal units, with transfusion rates of up to 9% reported [49]. These are largely given prophylactically, but there is little information on the optimal transfusion trigger and on the outcome of platelet transfusions [44]. Andrew and colleagues showed, in a randomized controlled trial, that there was no benefit of transfusing preterm babies with a platelet count between 50 and 150×10^9/l in order to reduce the incidence or extension of intracranial haemorrhage [50]. Below this level, guidelines such as the BCSH [34] recommend a threshold of $20–30 \times 10^9$/l, depending on the clinical situation (see also Table 2). This contrasts with the situation in adults where there is evidence that in many settings it is safe to have a transfusion trigger as low as 10×10^9/l [51,52]. Currently, an observational study funded by the National Blood Service is being undertaken in the UK to look at reasons for transfusing neonates and the outcome of those who are transfused. Based on the findings, it may be possible, in the

future, to undertake a prospective trial of platelet transfusion triggers for neonates and to consider whether lower triggers are appropriate.

Older children

The appropriate use of red cell transfusions for older children has been studied in the acute use in Paediatric Intensive Care units (PICU), and in chronic use for children with β-thalassaemia major or complications of sickle cell disease. In PICU there is a wide variation in transfusion practice, with transfusion triggers ranging between 7 and 13 g/dl reported in one survey [53]. There are some data suggesting that children in intensive care may benefit from a restrictive transfusion strategy to minimize red cell transfusions, as has been previously shown for adults [54]. In a retrospective cohort study, Goodman and colleagues [55] showed that for children with haemoglobin levels of ≤ 9 g/dl, transfusions were associated with increased resource use, as a measure of morbidity. To investigate this further, a multicentre randomized study is ongoing to compare a restrictive with a liberal transfusion strategy for critically ill children [Transfusion Requirements in Pediatric Intensive Care Units (TRIPICU), funded by the Canadian Institutes of Health].

Children with sickle cell disease may benefit from transfusions in both acute and chronic situations, and from additive or exchange transfusion [56,57]. The indications for chronic transfusions in sickle cell disease have changed following the successful introduction of hydroxyurea treatment for some patients with recurrent chest syndrome or painful crises [57]. However, chronic transfusions continue to be the mainstay of treatment for both primary and secondary prevention of stroke in children [58,59], despite recent evidence suggesting that hydroxyurea may also have a role in these situations [60,61]. The second Stroke Prevention Trial in Sickle Cell Anaemia (STOP II) investigated whether chronic transfusions for primary stroke prevention could be safely stopped after at least 30 months in children who had not had an overt stroke and who had reverted to 'low risk' on the basis of transcranial Doppler (TCD) velocities following this period of treatment. This trial was halted early, in December 2004, after finding that following the discontinuation of transfusions, a significant number of children reverted to a 'high risk' range on TCD analysis and after two children also had a stroke. The current recommendation is to continue transfusing in this situation.

There are ongoing uncertainties regarding the role of preoperative transfusion for both children and adults with sickle cell disease in order to try to prevent postoperative sickle complications. There is little evidence in the literature [62], and the only randomized controlled trial showed that exchange transfusion to a sickle Hb percentage of less than 30% resulted in no fewer sickle-related complications than top-up transfusion to a Hb of 10 g/dl alone [63]. Some centres therefore top-up patients to 10 g/dl for all but the lowest-risk operations, whereas others are more restrictive in their approach. However, it is not clear as to whether preoperative transfusion is really of benefit for the majority of sickle cell patients, for many of whom this would be their only transfusion, and a National Blood Service-funded randomized study of preoperative transfusion vs. no transfusion (TAPS) will commence soon to address this issue.

It is worth noting that for tonsillectomies in small children with sickle cell disease, some transfusions are given mainly to raise the baseline Hb as a safety measure in the event of hidden secondary haemorrhage postdischarge, rather than primarily to prevent sickle-related complications.

Conclusions and future directions

Paediatric transfusion has many potential complications and special requirements, but limited evidence from randomized trials to guide practice. The overall trend is for a reduction in the use of red cells and FFP in many neonatal units, and it is important to encourage this by practical measures, such as the use of local guidelines, minimizing blood sampling frequency and volumes, using appropriate giving sets to minimize dead space, and by ensuring the availability of neonatal coagulation ranges. Education of both clinical and laboratory staff about paediatric transfusion is essential in order to minimize the selection of inappropriate components and to guide appropriate use. Discussion of the implications of transfusion, and the provision of appropriate information for parents and children, are also important (Fig. 1), although

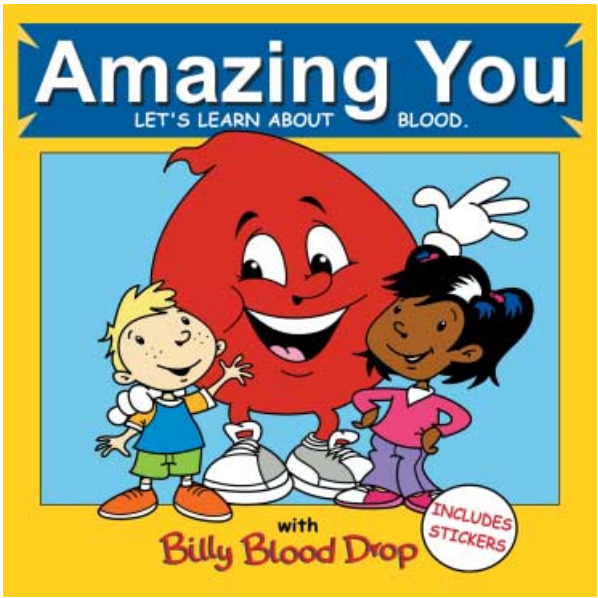

Fig. 1 Front cover of National Blood Service education booklet for younger children receiving a blood transfusion. Reproduced with permission from the National Blood Service, UK. ©National Blood Service.

in the UK formal parental consent for transfusion is not usually required. The reasons for transfusion and the outcome should be carefully documented in the medical notes.

Consideration also needs to be given to alternatives to transfusion. The use of erythropoietin to reduce top-transfusion of preterm neonates appears to have limited value [6,44]. However, perioperative cell salvage does have a useful role in selected paediatric surgery [38], and hydroxyurea has been used for many children with sickle cell disease (see above).

Much of the focus on special products for paediatric transfusion has so far been for neonatal provision. It is worth considering how this can be extended to older children, for example by the use of double-donation red cell apheresis. Trying to reduce alloimmunization, particularly of females, is an issue particularly for older children and for those with sickle cell disease. In the UK, concerns over risks from vCJD are having a significant impact on the specification of blood components for neonates and older children, and it is possible that this will have unforeseen negative effects, in addition to the significantly increased cost [64].

Despite the lack of evidence, current paediatric transfusion guidelines provide a good basis on which to continue developing consensus practice, which will, in turn, allow the generation of worthwhile observational data. However, there is a pressing need for more randomized studies, such as TRIPICU and PINT, to investigate paediatric transfusion triggers and outcome. Particularly challenging areas for study include the use of FFP and platelets in neonatal units and cardiac surgery. The clear aim for the future is to be able to give more evidence-based recommendations than is possible at present.

Acknowledgements

The illustration in Fig. 1 is reproduced with kind permission from the National Blood Service. I am grateful to my colleagues Irene Roberts, Simon Stanworth and Lorna Williamson for their helpful comments on the manuscript.

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