Transfusion guidelines for neonates and older children

This document updates the 'Guideline for the Administration of Blood Products: Transfusion of Infants and Neonates', published in 1994. In doing so it acknowledges changes in transfusion practice during the past decade, particularly in respect of safety issues and further published transfusion-related guidelines. The transfusion requirements of the neonate are recognized as unique, but there are other groups of children who are regularly transfused and who have very specific transfusion needs. There remains a lack of evidence for many transfusion practices in the neonatal period and childhood, making recommendations difficult in a number of areas.

The British Committee for Standards in Haematology published its last Guideline for the Administration of Blood Products regarding the Transfusion of Infants and Neonates in 1994 (British Committee for Standards in Haematology, 1994). This highlighted the lack of scientific evidence for many of the then widely accepted practices, which were often based on outdated information, particularly in neonatal transfusion. It sought to replace these with recommendations for which there was some scientific support or, at a minimum, defendable broad agreement. It influenced practice positively, but a number of transfusion guideline documents have been published in the last few years incorporating recommendations for transfusion practice in neonates and children. However, in the absence of controlled evaluation, many areas of uncertainty still remain. In addition, the National Health Service Executive (2002), entitled 'Better blood transfusion: appropriate use of blood' is as applicable to children as it is to adults.

Transfusion practice has advanced since 1994, particularly with respect to safety issues regarding the risk of transfusion-transmitted variant Creutzfeldt-Jacob disease (vCJD). (See the Guidelines for the use of fresh frozen plasma (FFP), cryoprecipitate and cryosupernatant (www.bcshguidelines.com) and the vCJD position statement in the document library of the UK Blood Services; http://www.transfusionguidelines.org.uk.) Although there is no current alternative to red cells and platelets from UK donors if the UK demand for these products is to be satisfied, sourcing FFP from donors residing in areas where bovine spongiform encephalopathy (BSE) and vCJD have never been endemic is more feasible. However, this may introduce other risks (e.g. if the prevalence of transfusion-transmissible diseases caused by known organisms is relatively high in such areas), but most of these diseases can be effectively eliminated from plasma by virus inactivation procedures. Although these procedures do not inactivate prions, by applying them to imported plasma the overall risks of transmitting infection (including vCJD) from treated products will be reduced.

Important changes in transfusion practice include:

- Leucocyte depletion (LD) of blood components, operative throughout the UK from 1 November 1999. This Guideline assumes that all cellular blood components, except granulocyte concentrates, are leucocyte depleted at the point of manufacture to comply with recent specifications (The Stationary Office, 2002) ($<5 \times 10^6$ white blood cells per component in at least 99% of components with 95% confidence). This is monitored by a statistical control process as the residual leucocyte content is not ascertained in all components issued (3·52 million in the UK in 2000/2001).
- The manufacture of fractionated pooled products from non-UK sourced plasma from November 1999.
- Although single donor plasma products (FFP, cryoprecipitate and cryosupernatant) are currently still prepared from UK-sourced plasma, FFP subjected to virus inactivating procedures ('virus inactivated plasma', VIP), such as photo-inactivation in the presence of methylene blue (MB FFP) or treatment with solvent detergent (SD FFP), has been available in limited quantities since 2002. However, virus inactivated cryoprecipitate is not yet available. Recipients of SD FFP have been infected with parvovirus B19 (a non-lipid enveloped virus which is less susceptible to inactivation) (Koenigbauer et al, 2000).
- The SD FFP is sourced from the USA where neither BSE nor vCJD are endemic. MB FFP, sourced from the USA, will become available from 2004. These are suited to children born after January 1996 who have therefore not been exposed to BSE in the food chain.
- Plasma treated with psoralen S-59 and UVA light has undergone clinical trials in the USA in patients with liver disease and those with rare single clotting factor deficiencies. No significant differences from other VIP have been noted. S-59-UVA-treated FFP is produced from single units of plasma and may become available in the UK soon.

Clinical advances have proceeded at an even greater pace. Progress in neonatal intensive care, extra corporeal membrane oxygenation (ECMO), cardiac bypass surgery, bone marrow and solid organ transplantation, and the management of haemoglobinopathies and malignancy means that any neonate or child requiring transfusion will be among the most intensively

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transfused of all hospital patients. Furthermore, they are likely to need highly specified products; the intensity of their transfusion, their age and potential life expectancy makes safety paramount.

This Guideline re-evaluates current transfusion practices, particularly evidence-based practices where they exist, and updates recommendations in existing guidelines in the light of developments in transfusion and clinical practice. Indications for transfusion, product selection, compatibility testing and administration of blood products, will be considered (see Appendix 1 for detailed recommendations).

1. Blood and blood component specification

1.1. General recommendations (fetuses, neonates, infants and children)

More precise product specifications for cellular and plasma components, including cryoprecipitate, are given in the 'Guidelines of the UK Blood Transfusion Services' (The Stationary Office, 2002). More details on granulocyte preparations are given in Section 3.2.4 of this Guideline.

1.1.1. Donors
Components for transfusion *in utero* or to children under 1 year of age must be prepared from blood donated by donors who have given at least one previous donation within the past 2 years, which was negative for all mandatory microbiological markers.

1.1.2. Leucocyte depletion
All components other than granulocytes should be leucocyte depleted (not more than 5×10^6 leucocytes per unit) at the time of manufacture (*level IV evidence, grade C recommendation*).

1.1.3. Cytomegalovirus
The 'Guidelines of the UK Transfusion Services' (The Stationary Office 2002) state that blood transfused in the first year of life should be cytomegalovirus (CMV) seronegative. The evidence for this is still under review, so this advice holds for the present. Other authorities state that components that have been leucodepleted to $<5 \times 10^6$/unit have a significant reduction in risk of CMV transmission (American Association of Blood Banks, 2000; Council of Europe, 2002: *level IIb evidence, grade A recommendation*). Those at greatest risk of transfusion transmitted CMV are fetuses and infants weighing under 1·5 kg, immunodeficient patients and stem cell transplant recipients. Some clinicians may prefer CMV seronegative components for recipients of haematopoietic stem cell transplants and patients with cellular immunodeficiency who are considered to be particularly susceptible to severe CMV infection.

Although the efficiency with which blood products in the UK are depleted of leucocytes is high, only a few products are directly tested for compliance with the specification. This means that there is no guarantee that an individual product has been sufficiently depleted, so that the use of products that are CMV seronegative is still recommended where CMV-free

products are indicated. However, in an emergency and where seronegative blood components are not available, transfusion of leucodepleted components is an acceptable, although less desirable, alternative (American Association of Blood Banks, 2000; Ronghe *et al*, 2002; The Stationary Office, 2002).

1.1.4. Irradiation
Blood components should be irradiated prior to transfusion in line with the Guidelines published by the British Committee for Standards in Haematology (1996a) (see also Appendix 2).

It is essential to irradiate all red cell and platelet components (with the exception of frozen red cells) for:

1 Intrauterine transfusion (IUT) (*level III evidence, grade B recommendation*).
2 Exchange transfusion (ET) of red cells after IUT (*level III evidence, grade B recommendation*).
3 Top-up transfusion after IUT (*level III evidence, grade B recommendation*).
4 When the donation is from a first- or second-degree relative or a human leucocyte antigen (HLA)-selected donor (*level III evidence, grade B recommendation*).
5 When the child has proven or suspected immunodeficiency (*level III evidence, grade B recommendation*).
6 Other indications as listed in the above Guidelines.

The component must be irradiated to a minimum dose of 25 Gy. For IUT and large volume transfusion (e.g. ET), the component should be used within 24 h of irradiation and within 5 d of donation (*level IV evidence, grade C recommendation*). Red cells for top-up transfusion may be irradiated at any time up to 14 d after collection, and thereafter stored for a further 14 d from irradiation (*level IV evidence, grade C recommendation*).

Platelets transfused *in utero* to treat alloimmune thrombocytopenia and platelet transfusions given after birth to infants who have received either red cells or platelets *in utero* should be irradiated. However, there is no need to irradiate other platelet transfusions in preterm or term infants, unless they are from first- or second-degree relatives (*level III evidence, grade B recommendation*).

All granulocytes should be irradiated for patients of any age and transfused as soon as possible after irradiation (*level III evidence, grade B recommendation*).

1.1.5. Plasma and platelet compatibility
Platelets should be ABO and RhD identical with the recipient. If this cannot be ensured, then compatible components lacking high titre anti-A or anti-B should be transfused to group A or B recipients. Group AB FFP, specifically for transfusion in the first year of life, may be given. For platelet and FFP transfusions, plasma compatibility should be ensured whenever possible. Both products contain enough red cell stroma to stimulate Rh immunization (*level IIb evidence, grade B recommendation* and *level IV evidence, grade B recommendation*). Therefore, RhD-negative girls for whom only RhD positive products are

available should receive anti-D immunoglobulin. The dose should be 50 IU anti-D per unit of FFP (200–300 ml) or per 500 ml of platelets transfused, or 250 IU per adult therapeutic dose of platelets (*c.* 250–350 ml, whether from a single apheresis donation or from a pack derived from a buffy coat pool from four donations). Components must not contain other clinically significant red cell antibodies.

1.1.6. Administration

All components should be transfused through a standard blood giving set with a screen filter (170–200 μ) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used. Micro-aggregate filters (40 μ) are not required for LD components.

1.2. Pretransfusion testing for neonates and infants within the first four postnatal months

Wherever possible, samples from both mother and infant should be obtained for initial ABO and RhD group determination.

Investigations on the maternal sample:

- ABO and RhD group.
- Screen for the presence of atypical red cell antibodies.

Investigations on the infant sample:

- ABO and RhD. ABO by cell group only, repeated on same sample if no historical result (a reverse group would detect passive maternal antibodies).
- Direct antiglobulin test (DAT) performed on the neonate's red cells.
- In the absence of maternal serum, screen infant's serum for atypical antibodies by an indirect antiglobulin technique (IAT).

A positive DAT on the neonate's red cells or an atypical red cell antibody in maternal or neonatal serum suggests possible haemolytic disease of the newborn (HDN). In such cases, special serological procedures will be necessary to allow selection of appropriate blood (*level IV evidence, grade C recommendation*).

1.2.1. Selection of blood component
Components should be

- Of the neonate's own ABO and RhD group, or an alternative compatible ABO and RhD group.
- Compatible with any ABO or atypical red cell antibody present in the maternal or neonatal plasma.
- An electronic cross-match may not select blood that is compatible with maternally derived ABO antibodies in the neonate's plasma. Therefore, it may not be appropriate to include neonatal samples in electronic cross-match protocols unless an appropriate algorithm has been created. ABO identical adult blood transfused to an infant with maternal anti-A or anti-B may haemolyse even if the pretransfusion DAT is negative, due to stronger ABO antigen expression

Table I. Choice of ABO group for blood products for administration to children.

Patient's ABO group	ABO group of blood product to be transfused		
	Red cells	Platelets	FFP*
O			
First choice	O	O	O
Second choice	–	A	A or B or AB
A			
First choice	A	A	A or AB
Second choice	O†	O†	–
B			
First choice	B	B‡	B or AB
Second choice	O†	A or O†	–
AB			
First choice	AB	AB‡	AB
Second choice	A, B	A	A
Third choice	O†		

*Group O fresh frozen plasma (FFP) should only be given to patients of group O. Although group AB FFP can be given to people of any ABO blood group, supplies are usually limited.
†Group O components which test negatively for 'high titre' anti-A and anti-B should be selected.
‡Platelet concentrates of group B or of group AB may not be available.

on adult cells (see Section 3.1.3; *level IV evidence, grade C recommendation*).

- Small volume transfusions can be given repeatedly over the first 4 months of life without further serological testing, provided that there are no atypical maternal red cell antibodies in the maternal/infant serum, and the infant's DAT is negative when first tested.
- If either the antibody screen and the DAT (or both) are positive, serological investigation or full compatibility testing will be necessary.

Infants rarely produce atypical red cell antibodies other than following repeated large volume transfusion and (possibly) the use of blood from donations collected up to 5 d before transfusion. It is only under these circumstances that repeat antibody screening of the recipient is advised (*level IIb evidence, grade B recommendation*). After the postnatal age of 4 months, compatibility tests should be conducted in accordance with national guidelines for pretransfusion testing in adult practice (British Committee for Standards in Haematology, 1996b, 2003a) (see Table I).

2. Intrauterine transfusion

2.1. Indications and aims

Intrauterine transfusions are usually administered only on specialized units. Intrauterine red cell transfusion is indicated to correct fetal anaemia caused by red cell alloimmunization (most important antigen-RhD followed by Rhc and K) or, less

commonly, for fetal parvovirus infection. Intrauterine platelet transfusions are indicated to correct fetal thrombocytopenia caused by platelet alloimmunization. The aims of IUT are (i) to prevent or treat fetal hydrops before the fetus can be delivered and (ii) to enable the pregnancy to advance to a gestational age that will ensure survival of the neonate (in practice, up to 36–37 weeks) with as few invasive procedures as possible (because of the risk of fetal loss). This is achieved by (i) starting the transfusion programme as late as safely possible but before hydrops develops and (ii) maximizing the intervals between transfusions, by transfusing as large a volume of red cells as is considered safe. Cell counting should be available close to fetal sampling or transfusion to provide an immediate haematocrit/haemoglobin or platelet count.

2.2. Component and procedure specification (see Table II)

2.2.1. Red cells preparations
Red cells preparations for IUT should

- be group O (low titre haemolysin) or ABO identical with the fetus (if known) and RhD negative. K-negative blood is recommended to reduce additional maternal alloimmunization risks. In exceptional cases, e.g. for haemolysis because of maternal anti-c, it may be necessary to give RhD positive, c-negative blood;
- be IAT-cross-match compatible with maternal serum and negative for the relevant antigen(s) determined by maternal antibody status.
- be <5 d old and in citrate phosphate dextrose (CPD) anticoagulant;
- be CMV seronegative;
- be irradiated as above (see Section 1.1.4);
- be have a haematocrit (packed cell volume, PCV) of up to but not more than 0·75;
- not be transfused straight from 4°C storage. As no specifically designed warming systems exist for the small volume of blood used for IUT, any active warming must be

carried out with great care and the blood product not exposed to temperatures higher than 30°C. Active warming may not be necessary if the infusion is conducted carefully and at an appropriate rate (see below);
- be in a volume calculated from the formula of Rodeck and Deans (1999):

$$\frac{\text{Desired PCV} - \text{Fetal PCV}}{\text{Donor PCV} - \text{Desired PCV}} \times \text{Fetoplacental BV,}$$

where BV is blood volume;
- be transfused at a rate of 5–10 ml/min.

2.2.2. Platelet preparations
Platelet preparations for IUT should

- be group O RhD negative and test negatively for high-titre anti-A or anti-B (i.e. have a low titre haemolysin) or group specific/compatible with maternal antibody;
- be human platelet-specific alloantigen (HPA) compatible with maternal antibody;
- preferably be collected by apheresis. A platelet concentrate derived from whole blood donations is less preferred;
- be irradiated as above (see Section 1.1.4);
- be concentrated to a platelet count of at least 2000×10^9/l;
- be warmed, if warmed at all, with extreme care. As the ambient temperature for storing platelet concentrates is 22°C, and as the recommended rate of infusion (see below) is slower than that for red cells, active warming may not be needed. If it is conducted, it should not be beyond 30°C;
- be in a volume calculated from the formula

$$\frac{\text{Desired platelet increment}}{\text{Platelet count of concentrate}} \times \text{Feto-placental BV}$$

- be transfused at a rate of 1–5 ml/min (transfused more slowly than red cells because of the increased risk of fetal circulatory stasis and asystole).

Compatible platelets should be available at the time of diagnostic fetal sampling for alloimmune thrombocytopenia, even if the primary purpose is not that of transfusion, because in the presence of severe fetal thrombocytopenia, fetal haemorrhage can be prevented by platelet transfusion.

Teflon-coated needles should be used because they are considered to allow samples of fetal blood which give more accurate cell counts (Welch *et al*, 1995: *level IIb evidence*, *grade B recommendation*).

3. Neonatal transfusion

3.1. Exchange transfusion

3.1.1. Indication and aims
Exchange transfusion may be used to manage severe anaemia at birth, particularly in the presence of heart failure, and to treat severe hyperbilirubinaemia, usually caused by HDN. In

Table II. Component volumes to be transfused to children and neonates.

Component	Volume
Red cell concentrates	
A. Exchange transfusion	
For a term infant	80–160 ml/kg
For a preterm infant	100–200 ml/kg
B. Top-up transfusion	Desired Hb (g/dl) − actual Hb × weight (kg) × 3 (usually 10–20 ml/kg)
Platelet concentrates	
Children weighing <15 kg	10–20 ml/kg
Children weighing >15 kg	Single apheresis unit/standard pool
Fresh frozen plasma	10–20 ml/kg
Cryoprecipitate	5 ml/kg or 15–30 kg = 5 units, >30 kg = 10 units

the treatment of HDN, the aim is to remove both the antibody-coated red cells and the excess bilirubin. Controversial indications such as metabolic disease, septicaemia and disseminated intravascular coagulation (DIC) have not been subjected to adequate clinical evaluation.

Exchange transfusion is a specialist procedure associated with a potential for serious adverse events. As such, it should be undertaken only by staff who are experienced in the procedure.

3.1.2. Principles

While there is, as yet, no consensus amongst neonatologists, plasma-reduced red cells with a haematocrit of 0·50–0·60 should be suitable for ET for both hyper-bilirubinaemia and severe anaemia (*level IV evidence, grade C recommendation*). Whole blood, with a haematocrit of 0·35–0·45 may result in a postexchange Hb of <12 g/dl in a severely anaemic baby and thus increase subsequent donor exposure. Packed red cells may have a haematocrit of up to 0·75, leading to an unacceptably high postexchange haematocrit.

Exchanging the estimated volume of the baby's blood in a 'single-volume exchange' will remove 75% of red cells, while a double-volume exchange (160–200 ml/kg, depending on gestation) removes 90% of the initial red cells. A double-volume exchange can remove 50% of available intravascular bilirubin.

The pH of a unit of whole blood or plasma-reduced red cells is around 7·0. This does not contribute to acidosis in the infant. Acidosis is more likely to be a result of underlying hypovolaemia, sepsis or hypoxia. 'Correction' of pH to physiological levels by the addition of buffer solutions is not indicated.

3.1.2.1. Component and procedure specifications. Red cells for ET should

- be group O or ABO compatible with maternal and neonatal plasma, RhD negative (or RhD identical with neonate);
- be negative for any red cell antigens to which the mother has antibodies;
- be IAT-cross-match compatible with maternal plasma;
- be 5 d old or less (to ensure optimal red cell function and low supernatant potassium levels);
- be collected into CPD anticoagulant;
- be CMV seronegative;
- be irradiated and transfused within 24 h of irradiation. Irradiation is essential if the infant has had a previous IUT and is recommended for all ETs (see Section 1.1.4 and Appendix 2). Irradiation for ET in absence of IUT is not essential if this would lead to clinically significant delay;
- have a haematocrit of 0·50–0·60;
- not be transfused straight from 4°C storage. If it is decided to warm the product prior to transfusion, extreme care must be taken to avoid over-heating. There is no easy way of achieving this for babies as the equipment designed to warm whole packs of blood warms it immediately prior to infusion; this arrangement is not suited to the intermittent bolus nature of ET procedures. Most clinical units allow

the infusate to approximate the ambient temperature while the blood is flowing from the primary pack through the syringes and filters before finally entering the patient's blood circulation;

- volume transfused is usually 80–160 ml/kg for a term infant and 100–200 ml/kg for a preterm infant (i.e. 1–2 × blood volume) depending on the clinical indication (see Table I; *all level IV evidence, grade C recommendation*).

3.1.3. ABO haemolytic disease of the newborn

Haemolysis may develop in fetuses and neonates who are ABO incompatible with their mother. Clinically significant haemolysis generally occurs only if the mother is group O and the infant group A (occasionally in group B babies). The haemolysis is due to the IgG anti-A or anti-B crossing the placenta and binding to the fetal red cells. Group A babies of group O mothers have a lower mean Hb and a higher mean cord bilirubin than in ABO compatible pairs. Nevertheless, clinically significant haemolysis is uncommon. The expression of A and B antigens on neonatal red cells is much weaker than on adult red cells which reduces the number of molecules of IgG which can bind, thus reducing or preventing haemolysis.

The diagnosis of HDN is complicated. Mothers with a high titre of IgG anti-A or anti-B are more likely to have affected babies but there is no direct relationship with the antibody titre. In addition, although severely affected babies will almost always have a positive DAT, this is not always the case. The preparation of eluates from DAT negative cells has been recommended but a positive DAT and positive eluate can be found in infants who have no evidence of haemolysis. Thus, at times the diagnosis of ABO HDN must be a diagnosis of exclusion: a relatively low cord blood Hb which continues to fall, a raised bilirubin level, ABO incompatibility with the mother and a positive DAT in the absence of any other alloantibodies. Spherocytes are a prominent feature on the blood smear. A high titre IgG anti-A or anti-B in the mother is supportive evidence but a low titre does not exclude the diagnosis.

If transfused with blood of their own group, group A or B babies who have maternal anti-A or anti-B in their plasma may convert to DAT positivity and develop haemolysis. This is due to the increased expression of A and B antigens on adult cells of those groups. Group O blood, compatible with the maternal plasma, should be used for transfusion (*level IV evidence, grade C recommendation*).

If an ET is required in ABO HDN, this should be with group O red cells with low titre plasma anti-A and anti-B, or with group O red cells suspended in AB plasma (*level IV evidence, grade C recommendation*).

3.2. Small volume transfusion

Most neonatal transfusions are small volumes (10–20 ml/kg), given to replace phlebotomy losses (see Tables II and III).

Table III. Suggested transfusion thresholds for infants under 4 months of age.

Transfusion of red blood cells	
Anaemia in the first 24 h	Hb 12 g/dl
	(Hct *c.* 0.36)
Cumulative blood loss in 1 week,	10% blood
neonate requiring intensive care	volume
Neonate receiving intensive care	Hb 12 g/dl
Acute blood loss	10%
Chronic oxygen dependency	Hb 11 g/dl
Late anaemia, stable patient	Hb 7 g/dl
Administration of platelets	
Preterm or term neonate, with bleeding	$50 \times 10^9/l$
Sick preterm or term infant, not bleeding	$30 \times 10^9/l$
Stable preterm or term infant, not bleeding	$20 \times 10^9/l$

Most departments have local guidelines with a range of haemoglobin values, depending on clinical status, at which to initiate transfusion.

Dedicating aliquots from a single donation of red cells (or aphaeresis platelets) to allow sequential transfusions from the same donor for neonates and small children who are likely to be repeatedly transfused is considered good practice. These must be transfused within the normal shelf-life (currently 35 d for red cells in additive solution, 5 d for platelets).

3.2.1. Guidelines for administration of red cells

It is impossible to produce clear evidence-based criteria for the administration of red cells in the neonatal period. However, clinicians who transfuse according to agreed local guidelines give fewer transfusions and it is recommended that local transfusion protocols be established in all neonatal units (Ross *et al*, 1989: *level Ib evidence, grade A recommendation*). Furthermore, there is no difference in outcome as determined by mortality or duration of hospital stay by transfusion approach. Table II gives proposals for neonatal red cell audit criteria. These are not 'transfusion triggers' *per se*, but represent standards against which individual nurseries can assess the appropriateness of their local transfusion policies (*level IV evidence, grade C recommendation*).

Surrogate markers of anaemia include respiratory irregularity, tachycardia, poor weight gain, lethargy, poor suck and increased blood lactate levels. All of these are susceptible to influence from confounding factors. Patients with a higher oxygen extraction ratio (>40%), a measure of adequacy of oxygen delivery, seem more likely to benefit from transfusion (Ross *et al*, 1989).

Although red cell transfusions may improve these parameters, there is no clear evidence of an associated improved outcome, such as reduced mortality or hospital stay. Furthermore, similar benefits may be obtained simply by volume expansion, implying that some of these surrogate markers may reflect a hypovolaemic state (Alverson *et al*, 1988).

3.2.1.1. Anaemia of prematurity. The aim of a top-up transfusion is to restore or maintain adequate tissue oxygen delivery without a marked increase in oxygen consumption (Alverson *et al*, 1988; Maier *et al*, 2000).

3.2.1.2. Oxygen dependency. Neonates with severe pulmonary disease are thought to benefit from a higher haemoglobin or haematocrit (0·40), which allows oxygen delivery to be optimized in the presence of underlying respiratory insufficiency. There is now some evidence that systemic oxygen delivery is improved and oxygen consumption decreased in infants with oxygen-dependent bronchopulmonary dysplasia by maintaining a haematocrit more than 0·40 (Alverson *et al*, 1988: *level Ib evidence, grade A recommendation*).

3.2.1.3. Erythropoietin. Recombinant human erythropoietin (EPO) may reduce red cell transfusion requirements in neonates. However, its effect appears to be relatively modest and does not reduce transfusion requirements within the first 2 weeks of life, when sick neonates are most transfusion dependent because of frequent blood sampling. The optimal dose, timing and nutritional support required during EPO therapy has yet to be defined and currently the routine use of EPO in this patient group is not recommended as similar reductions in blood use can probably be achieved by institution of appropriate transfusion protocols (Maier *et al*, 1994, 1998; Shannon *et al*, 1995; Franz & Pohlandt, 2001: *level IIb evidence, grade B recommendation*).

3.2.2. Fresh frozen plasma

Fresh frozen plasma should never be used as a simple volume replacement and it is not clearly superior to crystalloids or colloids in the management of neonatal hypotension. Routine administration to preterm infants to try to prevent periventricular haemorrhage (PVH) has been shown to confer no benefit and should therefore be avoided (Northern Neonatal Nursing Initiative Trial Group, 1996: *level IIb evidence, grade A recommendation*).

The clotting times of normal infant blood may be longer than those of adults, and those of premature infants (with reduced protein synthesis by the liver) may be even longer, even in the absence of further pathology (Male *et al*, 1999). Neonates with a significant coagulopathy [e.g. prothrombin time (PT) or activated partial thromboplastin time (APTT) ratio >1·5] and significant risk of bleeding (e.g. preterm and/or intubated, previous PVH) or who are about to undergo an invasive procedure should receive FFP at a dose of *c.* 15 ml/kg (*level IV evidence, grade C recommendation*). (Note, polycythaemia may lead the plasma of a citrated sample to be over-citrated and dilute.) Correction of the prolonged coagulation screen is unpredictable and this should therefore be rechecked following administration.

Fresh frozen plasma should not be used to treat polycythaemia unless there is a co-existent coagulopathy. FFP has not been proven to have clinical benefit when given

to septic patients in an attempt to improve immune function. Indeed the use of this component in sepsis may increase mortality, although the reason for this is not clear (Busund *et al*, 1993).

3.2.3. Platelets

Thrombocytopenia is common in sick preterm infants and is associated with an increased risk of severe periventricular bleeding (Andrew *et al*, 1987). However, the administration of platelets to manage moderate thrombocytopenia (platelets 50–100×10^9/l) did not appear to reduce the severity of bleeding (Andrew *et al*, 1993). In the absence of randomized, controlled trials in this patient group, recommendations for platelet transfusion must be made on the basis of clinical experience. Term infants are unlikely to bleed if the platelet count is maintained above 20×10^9/l but in small, preterm babies a higher threshold is generally recommended, particularly during the first few days when the risk of PVH is highest or if there is a co-existent coagulopathy (*level IV evidence, grade C recommendation*). In neonatal alloimmune thrombo-cytopenia, HPA-compatible platelets will be required, in addition to high dose intravenous immunoglobulin. In these patients, a minimum platelet count of 30×10^9/l is recommended because the HPA antibody can impair platelet function (*level IV evidence, grade C recommendation*) (see also British Committee for Standards in Haematology, 2003b; Table III).

3.2.4. Granuloctye concentrate

3.2.4.1. Production and storage.
Granulocyte concentrates obtained by centrifugation of refrigerated whole blood units are of poor function and generally yield inadequate doses. They should be obtained by centrifugation leucapheresis. If the donor is not preconditioned, this product is referred to as unstimulated granulocytes. However, it is generally impossible to obtain an adequate dose without the use of steroids and/or granulocyte-colony stimulating factor (G-CSF) to precondition the donor. In some UK centres, family members and friends who volunteer may, having given informed consent, be pretreated with G-CSF and dexamethasone to increase the yield (mobilized or stimulated granulocytes) (Engelfriet *et al*, 2000; Murphy *et al*, 2000).

Granulocytes should be stored in the same donor's citrate-anticoagulated plasma at room temperature and kept unagitated. They should be administered within 12 h of preparation. Storage for more than 8–12 h is associated with marked loss of function. Close liaison with the blood transfusion centre is essential to ensure that mandatory virology testing can be completed in time to allow infusion of a potentially effective component.

3.2.4.2. Indications for granulocyte transfusion.
Neonates with severe sepsis, who are deteriorating despite antibiotics and who have severe neutropenia for more than 24 h may benefit from granulocyte transfusion. However, these patients may also respond to the administration of G-CSF and currently it is not clear which of these approaches is more effective.

3.3. Component specification and procedure

3.3.1 Red cells for small volume transfusion
Red cells for small volume transfusion should

- be ABO compatible with mother and infant, and infant's RhD group (or RhD negative) (see Table I for ABO group selection of all components);
- be IAT compatible with maternal plasma (if available) or neonate's plasma for first transfusion (and subsequent transfusions up to four postnatal months if atypical maternal antibodies present);
- be 35 d old or less (if in SAG-M or similar additive system) or 28 d old or less (if in CPD) (*level Ia evidence, grade A recommendation*);
- have a haematocrit of 0·50–0·70;
- be irradiated if appropriate (see Section 1.1.4);
- usually be infused in a volume of 10–20 ml/kg;
- be aliquotted donations (pedipack) from a single unit dedicated to one infant (*level Ib evidence, grade B recommendation*).

3.3.2. Platelets for neonatal transfusion
Platelets for neonatal transfusion should

- be ABO identical or compatible (Table I): RhD identical or compatible;
- be HPA compatible in infants with alloimmune thrombo-cytopenia;
- be produced by standard techniques without further concentration;
- be irradiated if appropriate;
- usually be infused in a volume of 10–20 ml/kg (see Table II).

3.3.3. Fresh frozen plasma for neonatal transfusion
Fresh frozen plasma for neonatal transfusion should

- be group AB, or compatible with recipient's ABO red cell antigens (see Table I);
- usually be infused in a volume of 10–20 ml/kg (see Table II).

Virus inactivated plasma should be used for the treatment of patients with inherited coagulation deficiencies where no pathogen-inactivated (PI) factor concentrate is available (United Kingdom Haemophilia Centre Directors' Organisation, 1997). In other children the decision to use a PI-FFP rests with individual clinicians. Coagulation factor levels are lower in PI-FFP than untreated FFP. In MB-FFP, fibrinogen and factor VIII (FVIII) levels can be as low as 65% and 67% respectively. Other coagulation factors are generally present at

>75% normal activity. In SD FFP and S-59-UVA-FFP, coagulation factor levels are >75% and usually in the range of 80–95%.

3.3.4. Granulocytes: dose and duration of therapy

The suggested dose is 1–2×10^9 granulocytes/kg (Englefriet et al, 2000: level IIa evidence, grade B recommendation). The component must be ABO compatible with the recipient (as it is heavily contaminated with red cells), RhD compatible (RhD negative for RhD negative females) and irradiated to a minimum dose of 25 Gy prior to administration. It should also be CMV seronegative if appropriate (see Sections 1.1.3 and 5.1). The optimal duration of therapy is unclear but two or more daily infusions of an appropriate dose have been associated with improved outcome (Englefriet et al, 2000).

3.4. Special indications for blood products

3.4.1. Partial exchange transfusion for polycythaemia

In the newborn, the whole blood viscosity increases exponentially above a haematocrit of 0·65 and is particularly marked as the haematocrit exceeds 0·68. Hyperviscosity is associated with an increased risk of thrombosis and cardiac failure. Reduction of the haematocrit with partial ET does not appear to correlate directly with a reduction in morbidity. However, in the presence of symptomatic hyperviscosity, partial ET to reduce the haematocrit to 0·55 or below may be beneficial (level IV evidence, grade C recommendation). Crystalloid is an effective exchange fluid and controlled studies show no additional benefit when FFP or albumin is employed (level Ib evidence, grade A recommendation). However, if the baby is hypoalbuminaemic then dilutional exchange performed with 4·5% albumin will benefit the hypoalbuminaemia. The formula for calculating the volume (in ml) is:

$$\frac{\text{Blood volume} \times \text{Observed PCV} - \text{Desired PCV}}{\text{Observed PCV}}.$$

3.4.2. Use of albumin, synthetic colloids and crystalloids

Albumin administration may be associated with an excess mortality in adult patients (Cochrane Injuries Group Albumin Reviewers, 1998). A similar analysis of paediatric practice is not available. Albumin is not clearly superior to crystalloids in the management of hypovolaemic hypotension and does not significantly alter the respiratory status of hypoalbuminaemic sick preterm infants (So et al, 1997). Low molecular weight hydroxyethyl starch (hetastarch) appears as effective as albumin for volume replacement in neonates undergoing cardiopulmonary bypass, but when given at volumes more than 20 ml/kg may lead to a prolongation of the PT (not evidently associated with clinical bleeding), and close laboratory and clinical monitoring is then advised. Gelatin solution (Haemaccel, Beacon Pharmaceuticals, Tunbridge Wells, UK) has been shown to maintain the colloid osmotic pressure and the albumin level less effectively than 4·5% albumin in

neonates undergoing major surgery, but without an evident increase in morbidity or mortality.

Severe hypoalbuminaemia may be associated with marked peripheral oedema and respiratory distress and hypoalbuminaemic infants have an increased mortality. However, it is not clear that this relationship is causal, and there is no evidence that simply increasing the albumin level by albumin infusion positively affects the outcome.

3.4.3. Transfusion in necrotizing enterocolitis

Infants with necrotizing enterocolitis (NEC) may occasionally be systemically infected with neuraminidase-producing organisms, such as Clostridium sp. Neuraminidase can strip sialic acid residues from red cell sialoglycoproteins exposing the T-crypto antigen; a state commonly known as 'T-activation'. T-activation can be detected simply and rapidly using a commercial lectin panel. Adult (but not neonatal plasma) almost invariably contains anti-T, a potentially haemolytic IgM antibody. There is currently no consensus either with respect to the frequency of T-activation or the clinical significance of this finding in infants with NEC (Eder & Manno, 2001; Ramasethu & Luban, 2001).

It is recommended that patients with NEC be transfused with red cells in SAG-M as this is relatively plasma-free. Platelets, FFP and/or cryoprecipitate should only be administered when clearly indicated. Any patient with NEC who develops haemolysis, should be investigated to determine the cause of this. This should include a lectin test to look for T-activation. Where it is felt that T-activation is the likely cause, then an ET may be necessary. There is support but no consensus for routine provision of 'low-titre anti-T' plasma and platelet product for patients with T-activation. Access to these rare products is limited.

4. Transfusion support for children with haemoglobinopathies

4.1. General considerations

4.1.1. Children with haemoglobinopathies

These children are not just frequently transfused, but are possible future candidates for haemopoietic stem cell transplantation (SCT). Although some clinicians consider blood products that have been depleted to $<5 \times 10^6$ leucocytes per unit to be CMV-safe (see Section 1.1.3), others consider that more data are needed to demonstrate whether leucodepleted or CMV-seronegative components are the best option for minimizing transfusion-transmitted CMV after SCT (see Table IV; Section 5.1).

All children on regular transfusions should be vaccinated against hepatitis B as early as possible. Those on chronic transfusion therapy, particularly those with haemoglobinopathies, but also those with congenital dyserythropoietic anaemia, aplastic anaemia and other bone marrow failure syndromes, should have an extended red cell phenotype [Rh

Table IV. Indications for transfusion in children with sickle cell disease.

Top-up
Splenic sequestration*
Hepatic sequestration*
Aplastic crises*
Exchange transfusion
Chest syndrome*
Stroke*
Priapism*
Hepatic failure*
Mesenteric syndrome†
Hypertransfusion
Stroke (to prevent recurrence)*
Renal failure (to prevent/delay deterioration)†
Chronic sickle lung disease†
Osteonecrosis‡
Leg ulcers‡
Surgery§
Selected patients pre-operatively (e.g. joint replacement)

Using data from Davies and Roberts-Harewood (1997).
*Proven value.
†May help.
‡No proof of value shown yet.
§See Section 4.2.2.

and Kell; see also Section 4.3 for sickle cell disease (SCD)] performed prior to, or as soon as possible after, commencing regular transfusions. Reviews of the literature addressing allogeneic red cell and plasma transfusions in children have been published recently (Hume, 1996; Hume *et al*, 1997: *level Ib evidence, grade A recommendation*).

4.1.2. Volume of blood for top-up (standard) transfusion
A commonly used formula for determining the volume of packed red cells for top-up (standard) transfusion in infants and children is:

$$\text{Desired Hb (g/dl)} - \text{Actual Hb} \times \text{Weight (kg)} \times 3.$$

The recommended rate of transfusion of red cell products is *c.* 5 ml/kg/h.

4.1.3. Acceptable ABO group
Acceptable ABO blood groups for red cell transfusion (see Table I).

4.2. Indications and aims

4.2.1. Thalassaemia major
By definition all patients with thalassaemia major are transfusion dependent. Transfusion therapy is determined by the degree of anaemia and evidence of failure to thrive. Most children start transfusion when their haemoglobin concentration falls below 6 g/dl.

Aim: current guidelines (Cazzola *et al*, 1997: *level IIb, grade B recommendation*; Prati, 2000: *level IV evidence, grade C*

recommendation) and the new Thalassaemia International Federation guidelines (Olivieri, 1999: *level IIa evidence, grade B recommendation*) recommend:

- maintaining an *average* Hb of 12 g/dl;
- maintaining a *pretransfusion* Hb of 9–10 g/dl;
- that transfusion should prevent marrow hyperplasia, skeletal changes and organomegaly;
- red cell requirements should be adjusted to accommodate growth and hypersplenism considered if red cell requirements increase unexpectedly;
- iron chelation therapy should be considered after 10 transfusions and started once the ferritin is more than 1000 µg/l (if possible starting after 2 years of age) (Olivieri, 1999: *level IIa evidence, grade B recommendation*).

4.2.2. Sickle cell disease
Red cell transfusion in children with SCD (Ohene-Frempong, 2001; Telen, 2001) should not be routine but reserved for specific indications (*level Ib evidence, grade A recommendation*; see Table IV).
When to use simple additive or top-up transfusion in SCD:

- splenic or hepatic sequestration;
- aplastic crisis.

Aim: To raise the haemoglobin concentration to the child's normal steady state (the haemoglobin should never be raised acutely to >10 g/dl, as this is likely to cause an increase in blood viscosity).
When to use ET in SCD (Schmalzer *et al*, 1987; Emre *et al*, 1995):

- acute chest syndrome (*level IV evidence, grade C recommendation*). The aim is to reduce sickling and increase oxygen carriage with out an increase in viscosity;
- stroke; priapism (see Table II).

When to use hypertransfusion in SCD:

- patients on regular transfusions to prevent recurrence of stroke (Pegelow *et al*, 1995: *level IIa evidence, grade B recommendation*);
- of probable value to delay or prevent deterioration in end organ failure (e.g. chronic sickle lung);
- to prevent the development of stroke in children with SCD with Doppler and/or magnetic resonance imaging evidence of cerebro-vascular infarction/haemorrhage in the absence of clinical evidence of stroke (Miller *et al*, 1992: *level III evidence, grade C recommendation*; Adams *et al*, 1998: *level Ib evidence, grade A recommendation*).

Aim: To maintain the percentage of sickle haemoglobin (HbS) below 25% and the Hb between 10·0 and 14·5 g/dl. After 3 years a less intensive regimen maintaining the HbS at ≤50% may be sufficient for stroke prevention (Adams *et al*, 1998: *level Ib evidence, grade A recommendation*; Cohen *et al*, 1992: *level Ib evidence, grade B recommendation*).

Transfusion and surgery in SCD (Riddington & Williamson, 2001). It is standard practice in Europe and North America to transfuse children with SCD preoperatively despite lack of evidence. Based on observational studies (Koshy *et al*, 1995: *level Ib evidence, grade A recommendation*; Griffin & Buchanan, 1993: *level III evidence, grade B recommendation*) and one large randomized controlled study (Vichinsky *et al*, 1995: *level IIb evidence, grade B recommendation*),

- top-up transfusion aiming for Hb 8–10 g/dl is as effective as ET and may be safer (Vichinsky *et al*, 1995: *level IIb evidence, grade B recommendation*);
- minor and straightforward procedures (e.g. tonsillectomy, possibly cholecystectomy) can be safely undertaken without transfusion in most patients (Roberts-Harewood *et al*, 1997: *level III evidence, grade B recommendation*; Hatley *et al*, 1995: *level IV evidence, grade C recommendation*; Haberkern *et al*, 1997: *level Ib evidence, grade A recommendation*);
- transfusion should be performed preoperatively for major procedures (e.g. hip or knee replacement, organ transplantation, eye surgery and considered for major abdominal surgery).

Exchange transfusion in SCD. Reducing the percentage of HbS in the blood of children in the acute situation to 20% or less requires a total exchange of 1·5 to twice their blood volume. When conducted manually this generally requires two to three procedures; but automated cell separation enables the exchange to be completed in one procedure.

Normal saline (not FFP or albumin) should be used as volume replacement at the beginning of the exchange prior to starting venesection to avoid dropping the circulating blood volume. ET may also be used to minimize iron overload in patients on regular transfusions (Cohen *et al*, 1992: *level IIb evidence, grade B recommendation*; Kim *et al*, 1994: *level IIb evidence, grade B recommendation*).

4.3. Red cell specification for transfusion in thalassaemia and SCD (see also Table IV)

Such patients should be extensively phenotyped for red cell antigens (Rh, K in thalasaemia; Rh K, Fy, Jk and MNS in SCD) before the first transfusion. This is to facilitate selection of appropriate products should they become necessary, and to minimize alloimmunization (Singer *et al*, 2000: *level IIb evidence, grade B recommendation*; Olujohungbe *et al*, 2001: *level III evidence, grade B recommendation*; Davies & Roberts-Harewood, 1997: *level IIa evidence, grade B recommendation*; Vichinsky *et al*, 2001: *level IIb evidence, grade B recommendation*). All S− and s− patients should be typed for U.

Red cell preparations for thalassaemia and SCD should

- be ABO compatible (see Table I);
- be matched for Rh and K antigens (two-third of antibodies are in the Rh or K system and may be transient leading to a risk of delayed haemolytic transfusion reaction). The Ro

(cDe) genotype is common in people of Afro-Caribbean origin: all individuals phenotypically Ro must be transfused with C-negative and E-negative blood. This can be provided from rr or Ro red cells; Ro is to be preferred if available as rr blood should, whenever possible, be reserved for D-negative patients;

- be 35 d old or less (if collected into SAG-M or similar additive system) or 28 d old or less (if collected into CPD); there is no overall advantage in using 'neocytes' for top-up transfusion (Collins *et al*, 1994; Spanos *et al*, 1996: *level IIb evidence, grade B recommendation*).
- be tested for HbS prior to transfusion, as sickle-trait positive red cells should not be transfused;
- be CMV negative if appropriate (see Section 1.1.3).

5. Transfusion support for haemopoietic SCT, aplastic anaemia and malignancies

5.1. General points

All children with aplastic anaemia, or who are being treated with high-dose chemotherapy and/or radiotherapy may become candidates for SCT. While some clinicians consider components that have been depleted to $<5 \times 10^6$ leucocytes per unit to be CMV-safe (see Section 1.1.3), not all SCT centres agree (see Section 4.1.1).

Irradiation of blood products is not necessary in children receiving chemotherapy for leukaemia or solid tumours with the exceptions listed in Section 5.3.1.

5.2. Indications for transfusion

5.2.1. Red cells

There are no controlled trials upon which to base decisions about red cell transfusions in this group of children. The decision therefore depends on clinical judgement, taking into account the child's general condition, the presence or absence of bleeding and whether or not there are signs of haematological recovery. For children with aplasia, red cell transfusions are usually reserved for symptomatic patients with Hb values <7 g/dl, as sensitization to large numbers of transfusions reduces the chance of a successful outcome. The introduction of universal LD in the UK appears likely to reduce this risk (Saarinen *et al*, 1993; Williamson, 2000: *level III evidence, grade B recommendation*; *level Ib evidence, grade A recommendation*).

5.2.2. Platelets

In the absence of evidence-based guidelines for children, Table V reflects current recommended practice in children (Hume, 1996: *level IIb evidence, grade B recommendation*; Cahill & Lilleyman, 1998: *level IV evidence, grade C recommendation*; Ancliff & Machin, 1998: *level IV evidence, grade C recommendation*; Howard *et al*, 2000: *level III evidence, grade B recommendation*) and in adults (National Institutes of Health,

Table V. Indications for prophylactic platelet transfusion in children with thrombocytopenia as a result of reduced production.

Platelet count $<10 \times 10^9$/l
Platelet count $<20 \times 10^9$/l and one or more of the following
Severe mucositis
Disseminated intravascular coagulation (DIC)
Anticoagulant therapy
Platelets likely to fall $<10 \times 10^9$/l before next evaluation
Risk of bleeding due to a local tumour infiltration
Platelet count $20–40 \times 10^9$/l and one or more of the following
DIC in association with induction therapy for leukaemia
Extreme hyperleucocytosis
Prior to lumbar puncture or central venous line insertion

Using data from Hume (1996).

1987; Norfolk *et al*, 1998: *level IV evidence, grade C recommendations*; Wandt *et al*, 1998: *level IIa, grade B recommendation*), as well as the recent evidence-based guidelines produced by the American Society of Clinical Oncology which almost exclusively refers to studies in adults (Schiffer *et al*, 2001: *level Ib evidence, grade A recommendation*). In children with aplasia, a restrictive policy with platelet transfusion is safe for long-term management (Sagmeister *et al*, 1999: *level IV evidence, grade C recommendation*). However, children with aplastic anaemia during and following treatment with ALG in particular may require intensive platelet support. In contrast, some paediatricians are prepared to conduct follow-up lumbar punctures on children with counts as low as 20×10^9/l, having not experienced unduly high adverse effects. (Note, this recommendation differs from that in the recent Guidelines for the transfusion of platelets (British Committee for Standards in Haematology, 2003b), where the recommended threshold value is 50×10^9/l.)

5.2.3. Granulocytes

There is no evidence to support the use of prophylactic granulocyte transfusions (Engelfriet *et al*, 2000: *level IV evidence, grade C recommendation*). Empirical data from some but not all studies (*level Ib evidence, grade A recommendation*) support their use in the setting of severe bacterial or fungal infection in neutropenic children (Englefriet *et al*, 2000: *level IV evidence, grade C recommendation*; Price *et al*, 2000: *level IV evidence, grade C recommendation*; Bhatia *et al*, 1994: *level III evidence, grade B recommendation*) and, after SCT, to reduce the incidence of infection (Hubel *et al*, 2001: *level III evidence, grade B evidence*), but they increase the risk of platelet refractoriness, and few SCT centres use them. Therapeutic granulocyte transfusions may have a role in patients with congenital neutrophil dysfunction or severe neutropenia who are suffering from severe bacterial infection, are clinically deteriorating and unlikely to recover in a week despite maximal supportive care, including cytokines (Price *et al*, 2000: *level IV evidence, grade C recommendation*). Patients who are likely to receive a sibling/parent allograft should not receive granulocytes from family donors (see Section 3.2.4.1). The

efficacy of granulocytes collected from G-CSF-stimulated donors may be superior and is currently being evaluated (Price *et al*, 2000; Hubel *et al*, 2001: *level IV evidence, grade C recommendations*).

5.3. Component specification

5.3.1. Irradiation of blood products
Irradiation of blood products (see Appendix 2)

- for 2 weeks before all types of SCT and during conditioning for all types of SCT whichever is longer;
- in allogeneic SCT, irradiation should continue indefinitely;
- in autologous SCT, irradiation should continue for 3 months post-SCT (6 months if total body irradiation (total body irradiation (TBI) given);
- for SCT in children with severe combined immunodeficiency (SCID), irradiation should continue for at least a year following SCT or until normal immune function has been achieved;
- for 7 d prior to harvesting of autologous bone marrow or peripheral blood stem cells (PBSCs);
- for children with Hodgkin's disease during treatment and thereafter the susceptibility to transfusion-associated graft *versus* host disease (GvHD) is now considered to be life-long (Williamson, 1998: *level IV evidence, grade C recommendation*);
- during treatment with fludarabine and for at least 2 years or until full recovery of cellular immune function (Williamson *et al*, 1996; Williamson, 1998: *level IV evidence, grade C recommendation*);
- where blood products from relatives are being used.

5.3.2. Red cell transfusion in SCT: specification
For patients who have received an ABO compatible SCT red cell components for transfusion should

- be ABO group compatible (see Table I);
- be RhD compatible (N.B. After SCT, RhD negative red cells are given if the patient is RhD negative and/or the donor is RhD negative.);
- be leucocyte depleted ($<5 \times 10^6$/unit) at the time of manufacture;
- CMV negative if appropriate (see Section 1.1.3);
- be irradiated to a minimum of 25 Gy if SCT imminent (see Section 5.3.1).

For patients who have received an ABO incompatible SCT, red cell components for transfusion should

- be group O (irrespective of the ABO group of SCT donor) until ABO antibodies to the donor ABO type are undetectable and the DAT is negative; thereafter red cells of the donor group are given.

ABO incompatibility between the patient and SCT donor may be major, minor or both. In major incompatibility, the

recipient has antibodies to the SCT donor red cells; in minor incompatibility, the SCT preparation from the donor has antibodies to recipient cells; in both major and minor incompatibility, the recipient's plasma contains antibodies to the donor's cells and the donor plasma contains antibodies to the recipient's cells (e.g. recipient group B and SCT donor group A). However, selection of group O red cells for transfusion following an ABO incompatible SCT (SCT donor group A or B; patient group O) is straightforward, as O red cells in SAGM contain only small quantities of plasma. However, if a group A or B SCT shows relatively slow engraftment of red cells and anti-A or anti-B antibodies are slow to disappear, group O preparations from donors who are negative for high-titre anti-A,B or suspended in saline, may be preferred (see Section 3.1.3).

5.3.3. Platelets: specification

- ABO compatible where possible (see Table I): in view of the risk of haemolysis where there is major ABO incompatibility (Duguid *et al*, 1999: *level IV evidence, grade C recommendation*).
- >After an ABO incompatible SCT; platelets of the recipient's ABO group should be given until there is conversion to the donor ABO group and ABO antibodies to the donor ABO group are undetectable. Thereafter give donor group.
- Rh-D compatible: RhD negative girls must receive RhD-negative platelets in view of the risk of sensitization by contaminating red cells; RhD-negative platelets are also recommended for RhD-negative boys wherever possible.
- After SCT, RhD negative platelets are given if the patient is RhD negative and/or the donor is RhD negative.
- CMV negative if appropriate (see Section 5.1).
- Irradiated to a minimum of 25 Gy if SCT imminent (see Section 5.3.1).
- Recommended volume of platelet concentrate is 10–20 ml/kg for children under 15 kg and an aphaeresis unit for children over 15 kg.

5.3.4. Granulocytes

- ABO compatible
- RhD compatible (RhD negative girls must receive RhD negative granulocytes).
- CMV negative if appropriate (see Section 1.1.3).
- Irradiated to a minimum of 25 Gy for all recipients.

5.3.5. Fresh frozen plasma after ABO incompatible SCT
After SCT from a major or a minor ABO mismatch, FFP of group AB should be given.

5.3.6. Components for bone marrow donors
Healthy children who act as bone marrow donors for their sibling(s) usually require blood transfusion to cover blood lost during the procedure. In older children (over 25 kg and >8 years old) autologous blood donation should be considered around 2 weeks prior to marrow/PBSC donation. Allogeneic blood transfused to the donor during the bone marrow harvest should be extensively phenotyped (Rh, K, Fy, Jk and MNS), irradiated and CMV-safe (see Section 4.1.1).

6. Transfusion support for cardiac surgery, ECMO and acquired coagulopathies

6.1. Cardiac surgery

Each year in the UK *c.* 3·5 thousand children undergo cardiac surgery. Of these, 72% are open heart or bypass operations. Many children are iron deficient; pre-operative assessment should therefore include iron status.

6.1.1. Red cells for cardiac surgery
A number of factors influence practice.

- There are some evidence that blood losses may be less when fresh blood (<48 h old) is transfused (Mohr *et al*, 1988; Manno *et al*, 1991; Chambers *et al*, 1996), but only in very small children (under 2 years old) undergoing complex procedures. The benefit of fresh whole blood in cardiac surgery cannot be considered proven (Hershey & Glas, 1992).
- Infants having bypass surgery are effectively undergoing ET. For infants, it is reasonable to apply the same specifications as would be used in ET, i.e. red cells <5 d of age and not collected into optimal additive solutions, because of theoretical concerns about toxicity of the additive solution (*grade C recommendation*).
- There is no evidence to suggest that the transfusion of blood collected in additive solutions is associated with detriment in children older than 6 months (*grade C recommendation*).
- Older blood can be used for those older than 1 year, although units <10 d old should be provided whenever possible to cover the intraoperative and immediate postoperative periods when large volumes may be given quickly (*grade C recommendation*).
- The choice of fluid for bypass circuit priming (colloid and red cells, whole blood, crystalloid) is partly determined by the size of the patient, the volume of the extracorporeal circuit and the starting haemoglobin concentration.

6.1.2. Pharmacological agents to reduce blood requirements

- Desmopressin (DDAVP) in children undergoing cardiac surgery (Reynolds *et al*, 1993). This has been shown to be of no benefit in reducing blood loss (*level Ib evidence*).
- High dose aprotinin appears to be of value in reducing blood loss only in patients undergoing complex primary procedures (e.g. transposition of the great arteries) or in

re-do procedures (Boldt *et al*, 1993; Carrel *et al*, 1998; Miller *et al*, 1998: *level II evidence, grade B recommendation*).

- Low dose aprotinin (e.g. 500 000 units in pump prime only) is ineffective.
- Tranexamic acid has been shown to reduce blood loss in children with cyanosis undergoing cardiac surgery and in those undergoing repeat procedures. A variety of dose regimes have been used, but a dose of 10 mg/kg followed by an infusion of 1 mg/kg/h in adults produces an appropriate inhibitory level of tranexamic acid throughout the procedure (Fiechtner *et al*, 2001: *level III evidence, grade B recommendation*).
- Vitamin K deficiency is common in cyanotic infants preoperatively and should be corrected (Urban *et al*, 1984: *level IIb evidence, grade B recommendation*).

6.1.3. Cell salvage and 'bloodless' surgery

- Cell salvage procedures should be encouraged. Red cells salvaged from the extracorporeal circuit at the end of bypass are safe and effective in reducing homologous transfusion (Friesen *et al*, 1993: *level III evidence, grade B recommendation*).
- Bloodless cardiac surgery using isovolaemic haemodilution and bloodless priming of the extracorporeal circuit has been carried out successfully in the children of Jehovah's Witnesses (Stein *et al*, 1991: *level III evidence, grade B recommendation*).
- Evidence is available from adult practice (Spence *et al*, 1992) to support acceptance of a lower postoperative Hb level of 7 g/dl (*level III evidence*), which should also be appropriate in children with good postoperative cardiac function. There is no evidence to suggest any benefit from attempting to maintain a postoperative Hb concentration within the normal range (*grade B recommendation*).

6.1.4. Cold-reacting antibodies

Cold-reacting antibodies are of no clinical significance, even in patients who will be rendered hypothermic, and therefore do not require to be detected on antibody screens.

6.1.5. Coagulation components for cardiac surgery

Bypass procedures induce a complex haemostatic defect, which has been well reviewed (Bevan, 1999: *level IV evidence*). Blood loss is higher in complex and 're-do' procedures and in children <1 year of age. Reduction in the size of the bypass circuit can significantly reduce FFP and platelet requirements (De Somer *et al*, 1996: *level III evidence, grade B recommendation*).

- The routine use of FFP is of no proven benefit in cardiac surgery. It offers no proven advantage unless there are documented derangements of coagulation after correction of excess heparinization. There is no place for 'formula' use of FFP (British Committee for Standards in Haematology,

1992; unpublished observations: *level IV evidence, grade C recommendation*).

- Neonates in particular may have significantly low coagulation factors prior to bypass, which are then lowered further by dilution (Kern *et al*, 1992; Chan *et al*, 1997: *level IV evidence*).
- Excess protamine has been identified as an important and controllable cause of excessive bleeding (DeLaria *et al*, 1994: *level IIa evidence*).
- Platelet transfusions may be useful for thrombocytopenic bleeding or where platelet function is thought to be impaired.
- Topical thrombin/fibrin glues are effective in reducing suture line bleeding. If products incorporating aprotinin are used then it should be borne in mind that these patients may mount an immune response similar to those receiving intravenous aprotinin, which may cause reactions at the time of subsequent exposure.

6.1.6. Irradiation for Di George's syndrome (see Appendix 2)

It is increasingly recognized that infants with a variety of congenital cardiac lesions have lesions of chromosome 22, i.e. are variants of Di George's syndrome. Dysmorphic infants with truncus or interrupted aortic arch who do not have all the features of Di George's syndrome and who need cardiac surgery should have irradiated cellular procedures until the syndrome has been excluded (*grade C recommendation*).

6.2. Extra corporeal membrane oxygenation

During this highly specialized respiratory support, children are anticoagulated with heparin and require regular monitoring of coagulation parameters and platelet count.

- The combination of coagulopathy from the primary illness, the haemostatic defects associated with ECMO and haemodilution contribute to a high risk of intracranial haemorrhage.
- Following the initial 'coating' prime with albumin, priming with whole blood, packed red cells or packed cells and FFP may be indicated, particularly in very small babies and in those with a pre-existing coagulopathy.
- Blood should be as fresh as possible, and not more than 5 d old, in order to minimize the risk of hyperkalaemia.
- Whole blood or semi-packed red cells will contain a significant amount of relatively fresh plasma containing useful levels of all factors other than FVIII and FV.
- Red cells in additive solution are not advised for priming in view of the concerns about the possible toxicity of the constituents.
- Platelet transfusions should be given to maintain the platelet count above 100×10^9/l and FFP given to manage excessive bleeding caused by documented coagulation factor deficiency.

- The fibrinogen level should be maintained above 0·8–1·0 g/l with cryoprecipitate 5 ml/kg.
- Antithrombin levels may be very low, and at least one group recommend antithrombin infusion to keep the levels adequate for heparin function (Urlesberger *et al*, 1996).
- A normal haematocrit (of around 0·45) has been associated with increased risk of clotting in the circuit and increased donor exposure, which may be reduced by lowering the haematocrit to *c*. 0·35 (Griffin *et al*, 1992: *level Ib evidence*). However, the optimal haematocrit has not been determined.

6.3. Congenital and acquired coagulopathies

6.3.1. Congenital coagulopathies

Congenital bleeding disorders are rare, but important to recognize in the bleeding infant.

- Where an infant presents unexpectedly with a bleeding diatheses requiring urgent treatment an adequate blood sample must be obtained for immediate testing prior to infusion of any blood product.
- If treatment cannot be delayed until the results of specific tests are available, VIP sourced from non-UK plasma may be given. A dose of 20 ml/kg should result in a rise of *c*. 20% in coagulation factor levels.
- FFP is not optimal therapy for the more common severe coagulopathies, and is not sufficient for a baby with severe haemophilia A or B.

6.3.2. Acquired coagulopathies

The important acquired coagulopathies in infants and small children are:

- vitamin K deficiency;
- disseminated intravascular coagulation;
- liver disease – liver failure;
- anticoagulant reversal.

6.3.2.1. Vitamin K deficiency (Baglin, 1998; Sutor et al, 1999; unpublished observations). Vitamin K is required for normal function of factors of II, VII, IX and X. Regimens for prevention and treatment of vitamin K deficiency have recently been published with the evidence base (*level IV evidence*).

- In the child with a coagulopathy caused by vitamin K deficiency without bleeding, intravenous vitamin K treatment is sufficient.
- The response to systemic vitamin K is rapid (within 30–120 min).
- In the presence of bleeding it is advisable to give, along with vitamin K, either FFP 10–20 ml/kg (preferably a VIP and sourced from non-UK plasma if age appropriate), or an intermediate purity FIX concentrate ('prothrombin complex concentrate', PCC), which contains factors II, IX and

X. If such a concentrate is used, consideration should be given to vaccinating the child/baby against hepatitis B.
- FIX concentrate ('PCC') used in this way has been shown to be effective for bleeding because of warfarin excess in adults, but there are no data in children with vitamin K deficiency to guide dosage (*level IV evidence, grade C recommendation*).
- It is important to repeat coagulation tests regularly over 24–48 h to ensure correction is complete.

6.3.2.2. Disseminated intravascular coagulation.

- The neonate is particularly vulnerable to the onset of DIC, perhaps because of the relative immaturity of the liver.
- While the primary aim should be to correct the underlying cause, FFP at a dose of 10–15 ml/kg, preferably pathogen-inactivated and sourced from non-UK plasma if the patient is of appropriate age, is indicated unless the coagulopathy is mild (coagulation times <1·5 × control) and the child is haemostatic.
- Cryoprecipitate at a dose of 5 ml/kg is indicated if the fibrinogen falls acutely to less than 0·8–1·0 g/l.
- Heat-treated pooled fibrinogen concentrates are at present unlicensed and not available in doses suitable for neonates.
- Platelet concentrates are indicated for significant thrombocytopenia (see Table III).
- DIC needs to be monitored frequently to guide appropriate blood product therapy.

6.3.2.3. Liver disease.

- Severe liver failure is usually accompanied by profound coagulation derangements, including hypo-fibrinogenaemia.
- These children will need blood product support with cryoprecipitate (if the fibrinogen is less than 0·8–1·0 g/l) and FFP, until the liver recovers or the child has a liver transplant.
- Lesser degrees of coagulation derangement in hepatic dysfunction may require no coagulation support unless invasive procedures are required.
- Liver units tend to be guided by the international normalized ratio (INR) and consider liver biopsy to be safe if the INR is <1·4 or the PT up to 4 s longer than the upper limit of the normal range. APTT and thrombin time are not normally relevant for decision making (McGill *et al*, 1990: *level IV evidence, grade C recommendation*).
- The response to FFP in liver disease is unpredictable and repeat coagulation testing should be carried out immediately following completion of the infusion. The merits of continuous FFP administration (e.g. 5 ml/kg/h) *versus* intermittent boluses have not been addressed.
- A platelet count of at least 50×10^9/l is recommended for liver biopsy (Grant & Neuberger, 1999), although a count of at least 70×10^9/l may be preferable, particularly in the presence of an underlying coagulopathy.
- An important factor in bleeding risk may be the experience of the operator (Gilmore *et al*, 1995: *level III evidence*).

6.3.2.4. Anticoagulation in children, and its reversal.

- There are few published data on anticoagulation in children.
- A single centre review of 319 children (Streif *et al*, 1999) includes useful guidelines for dosing strategies, noting that infants who have had a Fontan procedure require a smaller dose of warfarin to achieve the target INR than other children (*level III evidence, grade C recommendation*).
- Guidelines on oral anticoagulation produced by the British Committee for Standards in Haematology are based entirely on adult data, and there are no trials demonstrating that these guidelines are optimal for children (British Committee for Standards in Haematology, 1998: *level IV evidence*).
- The principles of anticoagulant reversal in children are the same as for adults: for children with an INR >8·0 without bleeding, satisfactory partial reversal is likely to be obtained with low dose vitamin K (at one-tenth of the therapeutic dose) given parenterally (Bolton-Maggs & Brook, 2002) or orally, although the data for this route are known only for adults (Crowther *et al*, 1998).
- The INR should be checked after 2–6 h, and further doses given as required.
- If a high INR is associated with bleeding immediate reversal can be obtained with FFP (pathogen inactivated) or theoretically with a FIX concentrate ('PCC') containing factors II, IX and X (FVII may be required in addition). However, there are no published data in children.

Children on oral anticoagulants may require dental extractions. Evidence in adults demonstrates that extractions may be safely carried out without stopping the anticoagulation providing the INR is within the therapeutic range and there is no gross gum pathology (Devani *et al*, 1998: *level IIa evidence*). Good local haemostatic modalities are sufficient under these circumstances (Saour *et al*, 1994; Blinder *et al*, 1999: *level IIa evidence, grade B recommendation*).

7. Autologous transfusion in children

7.1. Indications and aims

As in adult practice, autologous transfusion techniques are employed primarily with the intention of reducing allogeneic donor exposure.

Autologous predeposit should be considered for children undergoing elective surgical procedures, including bone marrow harvest, in which there is a reasonable expectation that blood will be transfused.

Normovolaemic haemodilution and red cell salvage may be useful as an alternative or an adjunct to autologous predonation to minimize red cell losses during surgery. These techniques are not addressed further here but details can be found in the Guidelines of the British Committee for Standards in Haematology (1993). The potential adverse effects of these procedures should be taken into account in discussing the options with the child and/or parents. Patients who predonate autologous blood are more likely than others to receive a transfusion as they are more likely to be anaemic at the time of surgery and tend to be transfused with their autologous units at a higher haematocrit.

The child must understand the nature of the procedure and be willing to co-operate. Informed consent must be obtained from the parents.

7.2. Autologous Predeposit

- This should be considered in children over 25 kg but is technically difficult below this weight.
- The iron status of the child should be considered.
- Children with no unstable cardiovascular or pulmonary problems and a Hb concentration of >11 g/dl can be considered for predeposit.
- The maximum volume drawn at each donation is 12% of the estimated blood volume. The volume of citrate anticoagulant in the pack should be adjusted as required to maintain the appropriate ratio of blood to anticoagulant.
- Packs for paediatric use, which contain 35 ml of anticoagulant for the withdrawal of 250 ml of blood, are available and should be used wherever possible. Packs with small gauge needles suitable for phlebotomy in children should be used, when available.
- In some children a 'leap-frog' technique has been used to ensure a more adequate collection of blood. In this, the oldest donation that has been collected is re-infused during the collection of a 'double-volume' unit to avoid excessive volume depletion and acute anaemia.
- It should be borne in mind that this exposes the child both to the risks of the donation and to the risk of transfusion. The transfusion of an autologous unit, while not carrying a risk of viral transmission (unless units have been mixed up) may still result in a potentially fatal septic transfusion reaction (Popovsky *et al*, 1995). If the predeposited blood is not used, it may be appropriate to give supplemental iron for a few weeks.

8. Blood handling and administration

The serious hazards of transfusion reporting scheme (Love *et al*, 2001; Stainsby *et al*, 2003) has shown that children as well as adults may be affected by transfusion errors, may suffer from immunological transfusion reactions and may develop transfusion-transmitted infections. There are a number of circumstances that may place infants and children at particular risk.

- Confusion of maternal and baby (or placental) samples at time of birth, perhaps because of prelabelling of sample tubes or failure to label a sample from the mother before drawing the placental sample.

- Newborn multiple births. Mistakes may occur due to transposition of samples, for example, due to placental sampling with allocation of the wrong placenta to a particular baby or due to confusion arising between laboratory and neonatal unit when the infants are finally named.
- Failure to apply wristbands, particularly in children who are too young to state their identity and date of birth.
- failure to communicate special transfusion needs during shared care. The particular risks facing patients who require irradiated products may be minimized by the issue of a special card recently developed by the British Committee for Standards in Haematology in collaboration with the National Blood Service Clinical Policies Group.

For these reasons, attention to the correct identification of the patient and product at all stages of the transfusion process is essential. Monitoring during transfusion is equally necessary in paediatric patients as in adults and perhaps more so in younger children who may be less able to communicate discomfort or anxiety (British Committee for Standards in Haematology, 1999).

Disclaimer

Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

Appendix 1

Key to evidence statements and grades of recommendations

The definitions of the types of evidence and the grading of recommendations used in this guideline originate and derived from the US Agency for Health Care Policy and Research.

Statements of evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials.

Ib Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendations

A Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib).

B Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels IIa, IIb, III).

C Requires evidence obtained from the expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).

Appendix 2

Summary of British Committee for Standards in Haematology Guidelines on recommendations for the irradiation of blood and blood products for transfusion as applied to neonates and children (British Committee for Standards in Haematology, 1996a)

IUT and ET
All blood for IUT should be irradiated. It is essential to irradiate blood for ET if there has been a previous IUT, or if the donation is from a first- or second-degree relative. For other ET cases irradiation is recommended provided that it does not unduly delay transfusion. For IUT and ET, blood should be transfused within 24 h of irradiation, and in any case at 5 d or less from collection.

Small volume transfusion
There is no necessity to irradiate blood for routine top-up transfusions of premature or term infants unless either there has been a previous IUT or the blood is from a first- or second-degree relative, in which case the blood should be irradiated.

Platelet transfusions
Irradiation should be performed on platelets transfused *in utero* to treat alloimmune thrombocytopenia, and on platelet transfusions given after birth to infants who have received either red cells or platelets *in utero*. However, there is no need to irradiate other platelet transfusions for preterm or term infants, unless they are from first- or second-degree relatives.

Granulocytes
All granulocytes should be irradiated for babies of any age, and transfused as soon as possible after irradiation.

Cardiac surgery
There is no need to irradiate red cells or platelets for infants undergoing cardiac surgery unless clinical or laboratory features suggest co-existing immunodeficiency. There needs to be a high index of suspicion. If in doubt, blood should be

irradiated until a definitive diagnosis is made. If Di George syndrome is confirmed, then irradiated products are essential.

Congenital and acquired immunodeficiency

All immunological deficiency states outlined, with the exception of chronic mucocutaneous candidiasis, should be considered as indications for irradiation of cellular blood products. Once a diagnosis of immunodeficiency has been suspected, irradiated products should be given while further diagnostic tests are being undertaken. There is no indication for the irradiation of cellular blood components for infants or children who are human immunodeficiency virus (HIV) antibody positive, or who have acquired immunodeficiency syndrome.

Acute leukaemia and bone marrow transplantation

It is not necessary to irradiate red cells or platelets for children with acute leukaemia, except for children receiving fludarabine and children receiving HLA-matched platelets or donations from first- or second-degree relatives. All recipients of allogeneic bone marrow or PBSC transplantation should receive gamma-irradiated blood products from the time of initiation of conditioning chemo/radiotherapy and this should be continued while the patient remains on GvHD prophylaxis, i.e. usually 6 months, or until the lymphocyte count is more than 1×10^9/l. It may be necessary to irradiate blood products for SCID for considerably longer (up to 2 years), and for patients with chronic GvHD, if there is evidence of immunosuppression. Blood transfused to bone marrow donors prior to or during the harvest should be irradiated.

Patients undergoing bone marrow or PBSC harvesting for future autologous re-infusion should only receive gamma-irradiated cellular blood products during and for 7 d before the bone marrow/stem cell harvest, to prevent the collection of viable allogeneic T lymphocytes that could withstand cryopreservation. All patients undergoing autologous bone marrow transplantation or PBSCT should then receive gamma-irradiated cellular blood products from the initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if TBI used).

All children with Hodgkin's disease (but not non-Hodgkin's lymphoma) and those receiving purine analogue drugs (fludarabine, cladribine and deoxycoforycin). It is not necessary to irradiate blood components for children with solid tumours, organ transplants, HIV or aplastic anaemia. However, the effects of new regimes of chemo- and immunotherapy must be monitored.

Components

Gamma irradiation is currently the only recommended method for transfusion-associated GvHD prevention. Leucodepletion by current filtration technology is inadequate for this purpose. For at-risk patients, all red cells, platelet and granulocyte transfusions should be irradiated, except for cryopreserved red cells after deglycerolization. It is not necessary to irradiate FFP, cryoprecipitate or fractionated plasma products. All

transfusions from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent. Likewise, all HLA-selected platelets should be irradiated, even if the patient is immunocompetent.

Red cells may be irradiated at any time up to 14 d after collection, and thereafter stored for a further 14 d from irradiation. Where the patient is at particular risk from hyperkalaemia, e.g. IUT or ET, it is recommended that red cells be transfused within 24 h of irradiation.

Platelets can be irradiated at any stage in their 5-d storage period and can thereafter be stored up to their normal shelf life of 5 d after collection. Granulocytes for all recipients should be irradiated as soon as possible after production and thereafter transfused with minimum delay.

British Committee for Standards in Haematology Transfusion Task Force: Writing group; Dr Brenda E. S. Gibson (Chair), Dr Audrey Todd, Prof. Irene Roberts, Dr Derwood Pamphilon, Prof. CharlesRodeck (representing RCOG), Dr Paula Bolton-Maggs, Dr Geoff Durbin (Royal College of Paediatrics and Child Health). Task Force Members; Dr J. Duguid (Chair), Dr F. Boulton, Dr H. Cohen, Dr N. Smith, Dr D. B. L. McClelland, Dr M. Rowley, Dr G. Turner.

References

Adams, R.J., McVie, V.C., Hsu, L., Files, B., Vichinsky, E., Pegelow, C., Abboud, M., Gallagher, D., Kutlar, A., Nichols, F.T., Bonds, D.R. & Brambilla, D. (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine*, **339**, 5–11.

Alverson, D.C., Isken, V.H. & Cohen, R.S. (1988) Effect of booster blood transfusions on oxygen utilisation in infants with bronchopulmonary dysplasia. *Journal of Pediatrics*, **113**, 722–726.

American Association of Blood Banks (2000) *Standards for Blood Banks and Transfusion Services*, 20th edn. AABB, Bethesda.

Ancliff, P.J. & Machin, S.J. (1998) Trigger factors for prophylactic platelet transfusion. *Blood Reviews*, **12**, 234–238.

Andrew, M., Castle, V., Saigal, S., Caster, C. & Kelton, J.G. (1987) Clinical impact of neonatal thrombocytopenia. *Journal of Pediatrics*, **110**, 457–464.

Andrew, M., Vegh, P., Caco, C., Kirpalani, H., Jeffries, A., Ohlsson, A., Watts, J., Sagial, S., Milner, R. & Wang, E.A. (1993) Randomised controlled trial of platelet transfusions in thrombocytopenic premature infants. *Journal of Pediatrics*, **123**, 285–291.

Baglin, T. (1998) Management of warfarin (Coumarin) overdose. *Blood Reviews*, **12**, 91–98.

Bevan, D.H. (1999) Cardiac bypass haemostasis: putting blood through the mill. *British Journal of Haematology*, **104**, 208–219.

Bhatia, S., McCullough, J., Perry, E.J., Clay, M., Ramsay, N.K.C. & Neglia, J.P. (1994) Granulocyte transfusions: efficacy in treating fungal infection in neutropenic patients following bone marrow transplantation. *Transfusion*, **34**, 226–232.

Blinder, D., Manor, Y., Martinowitz, U., Taicher, S. & Hashomer, T. (1999) Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. *Oral*

Surgery, Oral Medicine, Oral Pathology, Oral Radiology, & Endodontics, **88,** 137–140.

Boldt, J., Knothe, C., Zickmann, B., Wege, N., Dapper, F. & Hempelmann, G. (1993) Comparison of two aprotinin dosage regimens in pediatric patients having cardiac operations. Influence on platelet function and blood loss (see comments). *Journal of Thoracic and Cardiovascular Surgery*, **105,** 705–711.

Bolton-Maggs, P. & Brook, L. (2002) The use of vitamin K for reversal of over-warfarinization in children. *British Journal of Haematology*, **118,** 924.

British Committee for Standards in Haematology (1992) Working Party of the Blood Transfusion Task Force Guidelines for the use of fresh frozen plasma. *Transfusion Medicine*, **2,** 57–63.

British Committee for Standards in Haematology (1993) Blood Transfusion Task Force. Guidelines for autologous transfusion. I. Preoperative autologous donation. *Transfusion Medicine*, **3,** 307–316.

British Committee for Standards in Haematology (1994) Blood Transfusion Task Force. Guidelines for administration of blood products: transfusion of infants and neonates. *Transfusion Medicine*, **4,** 63–69.

British Committee for Standards in Haematology (1996a) Guidelines on gamma-irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease. *Transfusion Medicine*, **6,** 261–271.

British Committee for Standards in Haematology (1996b) Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. *Transfusion Medicine*, **6,** 273–283.

British Committee for Standards in Haematology (1998) Guidelines on oral anticoagulation: third edition. *British Journal of Haematology*, **101,** 374–387.

British Committee for Standards in Haematology (1999) Blood Transfusion Task Force. The administration of blood and components and the management of transfused patients. *Transfusion Medicine*, **9,** 227–238.

British Committee for Standards in Haematology (2003a) Guidelines for compatibility in blood transfusion laboratories. *Transfusion Medicine*, in press.

British Committee for Standards in Haematology (2003b) Guidelines for the use of platelet transfusions. *British Journal of Haematology*, **122,** 10–23.

Busund, R., Straume, B. & Revhaug, A. (1993) Fatal course of severe meningococcemia: clinical predictors and effect of transfusion therapy. *Critical Care Medicine*, **21,** 1699–1705.

Cahill, M.R. & Lilleyman, J.S. (1998) The rational use of platelet transfusions in children. *Seminars in Thrombosis and Hemostasis*, **24,** 567–575.

Carrel, T.P., Schwanda, M., Vogt, P.R. & Turina, M.I. (1998) Aprotinin in pediatric cardiac operations: a benefit in complex malformations and with high dose regimen only. *Annals of Thoracic Surgery*, **66,** 153–158.

Cazzola, M., Borgna-Pignatti, C., Locatelli, F., Ponchio, L., Beguin, Y. & De Stefano, P. (1997) A moderate transfusion regimen may reduce iron loading in β-thalassaemia major without producing excessive expansion of erythropoiesis. *Transfusion*, **37,** 135–140.

Chambers, L.A., Cohen, D.M. & Davis, J.T. (1996) Transfusion patterns in pediatric open heart surgery. *Transfusion*, **36,** 150–154.

Chan, A.K., Leaker, M., Burrows, F.A., Williams, W.G., Gruenwald, C.E., Whyte, L., Adams, M., Brooker, L.A., Adams, H., Mitchell, L. & Andrew, M. (1997) Coagulation and fibrinolytic profile of paediatric

patients undergoing cardiopulmonary bypass. *Thrombosis and Haemostasis*, **77,** 270–277 (published erratum appears in *Thrombosis and Haemostasis* 1997; 77: 1047).

Cochrane Injuries Group Albumin Reviewers (1998) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *British Medical Journal*, **317,** 235–240.

Cohen, A.R., Martin, M.B., Silber, J.H., Kim, H.C., Ohene-Frempong, K. & Schwartz, E. (1992) A modified transfusion program for prevention of stroke in sickle cell disease. *Blood*, **79,** 1657–1661.

Collins, A.F., Goncalves-Dias, C., Haddad, S., Talbot, R., Herst, R., Tyler, B.J., Zuber, E., Blanchette, V.S. & Olivieri, N.F. (1994) Comparison of a transfusion preparation of newly formed red cells and standard transfusions in patients with homozygous beta-thalassemia. *Transfusion*, **34,** 517–520.

Council of Europe (2002) *Guide to the Preparation, Use and Quality Assurance of Blood Components*, 8th edn. Council of Europe Publishing, Strasbourg.

Crowther, M., Donovan, D., Harrison, L., McGinnis, J. & Ginsberg, J. (1998) Low dose oral vitamin K reliably reverses overanticoagulation due to warfarin. *Thrombosis and Haemostasis*, **79,** 1116–1118.

Davies, S.C. & Roberts-Harewood, M. (1997) Blood transfusion in sickle cell disease. *Blood Reviews*, **11,** 57–71.

De Somer, F., Foubert, L., Poelaert, J., Dujardin, D., Van Nooten, G. & Francois, K. (1996) Low extracorporeal priming volumes for infants: a benefit? *Perfusion*, **11,** 455–460.

DeLaria, G.A., Tyner, J.J., Hayes, C.L. & Armstrong, B.W. (1994) Heparin-protamine mismatch. A controllable factor in bleeding after open heart surgery. *Archives of Surgery*, **129,** 944–951.

Devani, P., Lavery, K.M. & Howell, C.J. (1998) Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? (see comments). *British Journal of Oral and Maxillofacial Surgery*, **36,** 107–111.

Duguid, J.K., Minards, J. & Bolton-Maggs, P.H. (1999) Lesson of the week: incompatible plasma transfusions and haemolysis in children. *British Medical Journal*, **318,** 176–177.

Eder, A.F. & Manno, C.S. (2001) Does red cell T activation matter? *British Journal of Haematology*, **114,** 25–30.

Emre, U., Miller, S.T., Gutierez, M., Steiner, P., Rao, S.P. & Rao, M. (1995) Effect of transfusion in acute chest syndrome of sickle cell disease. *Journal of Pediatrics*, **127,** 901–904.

Engelfriet, C.P., Reesink, H.W. & Klein, H.G. (2000) International forum: granulocyte transfusions. *Vox Sanguinis*, **79,** 59–66.

Fiechtner, B.K., Nuttall, G.A., Johnson, M.E., Dong, Y., Sujirattanawimol, N., Oliver, Jr, W.C., Sarpal, R.S., Oyen, L.J. & Ereth, M.H. (2001) Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesthesia & Analgesia*, **92,** 1131–1136.

Franz, A.R. & Pohlandt, F. (2001) Red blood cell transfusion in very and extremely low birthweight infants under restrictive transfusion guidelines: is exogenous erythropoietin necessary? *Archives of Disease in Childhood Fetal & Neonatal Edition*, **84,** F96–F100.

Friesen, R.H., Tornabene, M.A. & Coleman, S.P. (1993) Blood conservation during pediatric cardiac surgery: ultrafiltration of the extracorporeal circuit volume after cardiopulmonary bypass. *Anesthesia & Analgesia*, **77,** 702–707.

Gilmore, I., Burroughs, A., Murray-Lyon, I., Williams, R., Jenkins, D. & Hopkins, A. (1995) Indications, methods and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut*, **36,** 437–441.

Grant, A. & Neuberger, J. (1999) Guidelines on the use of liver biopsy in clinical practice, British Society of Gastroenterology. *Gut*, **45**(Suppl. 4)**,** IV1–IV11.

Griffin, T.C. & Buchanan, G.R. (1993) Elective surgery in children with sickle cell disease without preoperative blood transfusion. *Journal of Pediatric Surgery*, **28,** 681–685.

Griffin, M.P., Minifee, P.K., Daeschner III, C.W. & Zwischenberger, J.B. (1992) Benefits of a lower haematocrit during extracorporeal membrane oxygenation? *American Journal of Diseases of Children*, **146,** 373–374.

Haberkern, C.M., Neumayr, L.D., Orringer, E.P., Earles, A.N., Robertson, S.M., Black, D., Abboud, M.R., Koshy, M., Idowu, O. & Vichinsky, E.P. (1997) Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. *Blood*, **89,** 1533–1542.

Hatley, R.M., Christ, D., Howell, C.F., Herline, A.J. & Gadacz, T.R. (1995) Laparoscopic cholecystectomy in children with sickle cell disease. *American Surgeon*, **61,** 169–171.

Hershey, M.D. & Glas, D.D. (1992) Con: whole blood transfusions are not useful in patients undergoing cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, **6,** 761–763.

Howard, S.C., Gajjar, A. & Ribeiro, R.C. (2000) Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. *Journal of the American Medical Association*, **284,** 2222–2224.

Hubel, K., Dale, D.C., Engert, A. & Liles, W.C. (2001) Current status of granulocyte (neutrophil) transfusion therapy for infectious diseases. *Journal of Infectious Diseases*, **183,** 321–328.

Hume, H.A. (1996) Transfusion Support of children with hematologic and oncologic disorders in clinical practice of transfusion medicine. In: *Clinical Practice of Transfusion Medicine*, 3rd edn (ed. by L.D. Petz, S.N., Swisher, S. Kleinman, R.K. Spence & R.G. Strauss), pp. 705–732. Churchill Livingstone, New York.

Hume, H.A., Kronick, J.B. & Blanchette, V.B. (1997) Review of the literature on allogeneic red blood cells and plasma transfusion in children. *Canadian Medical Association Journal*, **156,** S41–S49.

Kern, F.H., Morana, N.J., Sears, J.J. & Hickey, P.R. (1992) Coagulation defects in neonates during cardiopulmonary bypass (see comments). *Annals of Thoracic Surgery*, **54,** 541–546.

Kim, H.C., Dugan, N.P., Silber, J.H., Martin, M.B., Schwartz, E., Ohene-Frempong, K. & Cohen, A.R. (1994) Erythrocytapheresis therapy to reduce iron overload in chronically transfused patients with sickle cell disease. *Blood*, **83,** 1136–1142.

Koenigbauer, U.F., Eastlund, T. & Day, J.W. (2000) Clinical illness due to parvovirus B19 infection after infusion of solvent/detergent-treated pooled plasma. *Transfusion*, **40,** 1203–1206.

Koshy, M., Weiner, S.J., Miller, S.T., Sleeper, L.A., Vichinsky, E., Brown, A.K., Khakoo, Y. & Kinney, T.R. (1995) Surgery and anesthesia in sickle cell disease. *Blood*, **86,** 3676–3684.

Love, E.M., Jones, H., Williamson, L.M., Cohen, H., Todd, A., Soldan, K., Revill, J., Norfolk, D.R., Barbara, J., Atterbury, C.L.J. & Asher, D. (2001) *Serious Hazards of Transfusion Annual Report 1999–2000.* Serious Hazards of Transfusion Steering Group, Manchester, UK (ISBN 0 9532 789 3 X).

McGill, D., Rakela, J., Zinzsmeister, A. & Ott, B. (1990) A 21 year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology*, **99,** 1396–1400.

Maier, R.F., Obladen, M., Scigalla, P., Linderkamp, O., Duc, G., Heironimi, G., Halliday, H.L., Versmold, H.T., Moriette, G., Jorch, G., Verellwen, G., Semmekrot, B.A., Grauel, E.L., Holland, B.M. & Wardrop, C.A.J. (1994) The effect of epoietin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. European Multicentre Erythropoietin Study Group. *New England Journal of Medicine*, **330,** 1173–1178.

Maier, R.F., Obladen, M., Kattner, E., Natzschka, J., Messer, J., Regazzoni, B.M., Speer, C.P., Fellman, V., Grauel, E.L., Groneck, P., Wagner, M., Moriette, G., Salle, B.L., Verellen, G. & Scigalla, P. (1998) High- versus low-dose erythropoietin in extremely low birth weight infants. The European Multicenter rhEPO Study Group. *Journal of Pediatrics*, **132,** 866–870.

Maier, R.F., Sonntag, F., Walka, M., Liu, G., Metze, B.C. & Obladan, M. (2000) Changing practices of red blood cell transfusion in infants with birth weights less than 1000 g. *Journal of Pediatrics*, **136,** 220–224.

Male, C., Johnston, M., Sparling, C., Brooker, L., Andrew, M. & Massicotte, P. (1999) The influence of developmental haemostasis on the laboratory diagnosis and management of haemostatic disorders during infancy and childhood. *Clinics in Laboratory Medicine*, **19,** 39–69.

Manno, C.S., Hedberg, K.W., Kim, H.C., Bunin, G.R., Nicolson, S., Jobes, D., Schwartz, E. & Norwood, W.I. (1991) Comparison of the hemostatic effects of fresh whole blood, stored whole blood and components after open heart surgery in children. *Blood*, **77,** 930–936.

Miller, S.T., Jensen, D. & Rao, S.P. (1992) Less intensive long-term transfusion therapy for sickle cell anemia and cerebrovascular accident. *Journal of Pediatrics*, **120,** 54–57.

Miller, B.E., Tosone, S.R., Tam, V.K., Kanter, K.R., Guzzetta, N.A., Bailey, J.M. & Levy, J.H. (1998) Haematologic and economic impact of aprotinin in reoperative cardiac operations. *Annals of Thoracic Surgery*, **66,** 535–540.

Mohr, R., Martinowitz, U., Lavee, J., Amroch, D., Ramot, B. & Goor, D.A. (1988) The hemostatic effect of transfusing fresh whole blood versus platelet concentrates after cardiac operations. *Journal of Thoracic and Cardiovascular Surgery*, **96,** 530–534.

Murphy, M.F., Pamphilon, D. & Devereux, S. (2000) International forum: granulocyte transfusions. *Vox Sanguinis*, **79,** 61–62.

National Health Service Executive (2002) *Health Service Circular HSC 2002/009. Better Blood Transfusion: Appropriate Use of Blood*. Department of Health, UK. WWW document. URL. http://www.doh.gov.uk/bbt2/009hsc2002.pdf.

National Institutes of Health (1987) Consensus conference; platelet transfusion therapy. *Transfusion Medicine Review*, **1,** 195–200.

Norfolk, D.R., Ancliff, P.J., Contreras, M., Hunt, B.J., Machin, S.J., Murphy, W.G. & Williamson, L.M. (1998) Consensus conference on platelet transfusion. Royal College of Physicians of Edinburgh, 27–28 November 1997. *British Journal of Haematology*, **101,** 609–617.

Northern Neonatal Nursing Initiative Trial Group (1996) Randomised trial of prophylactic early fresh-frozen plasma, gelatin or glucose in pre-term babies: outcome at 2 years. *Lancet*, **348,** 229–232.

Ohene-Frempong, K. (2001) Indications for red cell transfusion in sickle cell disease. *Seminars in Hematology*, **38,** 5–13.

Olivieri, N.F. (1999) The β-thalassemias. *New England Journal of Medicine*, **341,** 99–109.

Olujohungbe, A., Hambleton, E., Stephens, L., Serjeant, B. & Serjeant, G. (2001) Red cell antibodies in patients with homozygous sickle cell

disease: a comparison of patients in Jamaica and the United Kingdom. *British Journal of Haematology*, **113,** 661–665.

Pegelow, C.H., Adams, R.J., McKie, V., Abboud, M., Berman, B., Miller, S.T., Olivieri, N., Vichinsky, E., Wang, W. & Brambilla, D. (1995) Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *Journal of Pediatrics*, **126,** 896–899.

Popovsky, M.A., Whitaker, B. & Arnold, N.L. (1995) Severe outcomes of allogeneic and autologous blood donations: frequency and characterisation. *Transfusion*, **35,** 734–737.

Prati, D. (2000) Benefits and complications of regular blood transfusion in patients with beta-thalassaemia major. *Vox Sanguinis*, **79,** 129–137.

Price, T.H., Bowden, R.A., Boeckh, M., Bux, J., Nelson, K., Liles, W.C. & Dale, D.C. (2000) Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in haemapoietic stem cell transplantation. *Blood*, **95,** 3302–3309.

Ramasethu, J. & Luban, N.L.C. (2001) T activation. *British Journal of Haematology*, **112,** 259–263.

Reynolds, L.M., Nicolson, S.C., Jobes, D.R., Steven, J.M., Norwood, W.I., McGonigle, M.E. & Manno, C.S. (1993) Desmopressin does not decrease bleeding after cardiac operation in young children. *Journal of Thoracic and Cardiovascular Surgery*, **106,** 954–958.

Riddington, C. & Williamson, L. (2001) Preoperative blood transfusions for sickle cell disease (Cochrane review). *Cochrane Database of Systematic Review*, **3,** CD003149.

Roberts-Harewood, M., Nokes, T.J.C., Taylor, P.C. & Davies, S.C. (1997) Adenotonsillectomy in sickle cell disease: is routine transfusion necessary? *British Journal Haematology*, **97**(Suppl. 1)**,** 75.

Rodeck, C.H. & Deans, A. (1999) Red cell allo-immunisation. In: *Fetal Medicine: Basic Science and Clinical Practice* (ed. by C.H. Rodeck & M.J. Whittle), pp. P785–P804. Churchill Livingstone, London.

Ronghe, M.D., Foot, A.B., Cornish, J.M., Steward, C.G., Carrington, D., Goulden, N., Marks, D.I. & Oakhill, A. (2002) The impact of transfusion of leucodepleted platelet concentrates on cytomegalovirus disease after allogeneic stem cell transplantation. *British Journal of Haematology*, **118,** 1124–1127.

Ross, M.P., Christensen, R.D., Rothstein, G., Koenig, J.M., Simmons, M.A., Noble, N.A. & Kimura, R.E. (1989) A randomized trial to develop criteria for administering erythrocyte transfusions to anemic preterm infants 1 to 3 months of age. *Journal of Perinatology*, **9,** 246–253.

Saarinen, U.M., Koskimies, S. & Myllyla, G. (1993) Systematic use of leukocyte-free blood components to prevent alloimmunization and platelet refractoriness in multitransfused children with cancer. *Vox Sanguinis*, **65,** 286–292.

Sagmeister, M., Oec, L. & Gmur, J. (1999) A restrictive platelet transfusion policy allowing long-term support of outpatients with severe aplastic anemia. *Blood*, **93,** 3124–3126.

Saour, J.N., Ali, H.A., Mammo, L.A. & Sieck, J.O. (1994) Dental procedures in patients receiving oral anticoagulation therapy. *Journal of Heart Valve Disease*, **3,** 315–317.

Schiffer, C.A., Anderson, K.C., Bennett, C.L., Bernstein, S., Elting, L.S., Goldsmith, M., Goldstein, M., Hume, H., McCullough, J.J., McIntyre, R.E., Powell, B.L., Rainey, J.M., Rowley, S.D., Rebulla, P., Troner, M.B. & Wagnon, A.H. for the American Society of Clinical Oncology (2001) Platelet transfusion for patients with cancer:

clinical practice guidelines of the American Society of Clinical Oncology. *Journal of Clinical Oncology*, **19,** 1519–1538.

Schmalzer, E.A., Lee, J.O., Brown, A.K., Usami, S. & Chien, S. (1987) Viscosity of mixtures of sickle and normal red cells at varying hematocrit levels: implications for transfusion. *Transfusion*, **27,** 228–233.

Shannon, K.M., Keith III, J.F., Mentzer, W.C., Ehrenkranz, R.A., Brown, M.S., Widness, J.A., Gleason, C.A., Bifano, E.M., Millard, D.D. & Davis, C.B. (1995) Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. *Pediatrics*, **95,** 1–8.

Singer, S.T., Wu, V., Mignacca, R., Kuypers, F.A., Morel, P. & Vichinsky, E.P. (2000) Alloimmunization and erythrocyte auto-immunization in transfusion-dependent thalassemia patients of predominantly Asian descent. *Blood*, **96,** 3369–3373.

So, K.W., Fok, T.F., Ng, P.C., Wong, W.W. & Cheung, K.L. (1997) Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. *Archives of Diseases of Children*, **76,** F43–F46.

Spanos, T., Ladis, V., Palamidou, F., Papassotiriou, I., Banagi, A., Premetis, E. & Kattamis, C. (1996) The impact of neocyte transfusion in the management of thalassemia. *Vox Sanguinis*, **70,** 217–223.

Spence, R.K., Alexander, J.B., DelRossi, A.J., Cernaianu, A.D., Cilley, Jr, J., Pello, M.J., Atabek, U., Camishion, R.C. & Vertrees, R.A. (1992) Transfusion guidelines for cardiovascular surgery: lessons learned from operations in Jehovah's Witnesses. *Journal of Vascular Surgery*, **16,** 825–831.

Stainsby, D., Jones, H., Knowles, S., Beatty, C., Revill, J., Cohen, H., Todd, A., Taylor, C., Davison, K. & Norfolk, D.R. (2003) *Serious Hazards of Transfusion Annual Report 2001–2002*. Serious Hazards of Transfusion Steering Group, Manchester, UK (ISBN 0 9532 789 5 6).

Stein, J.I., Gombotz, H., Rigler, B., Metzler, H., Suppan, C. & Beitzke, A. (1991) Open heart surgery in children of Jehovah's Witnesses: extreme hemodilution on cardiopulmonary bypass. *Pediatric Cardiology*, **12,** 170–174.

Streif, W., Andrew, M., Marzinotto, V., Massicotte, P., Chan, A.K., Julian, J.A. & Mitchell, L. (1999) Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood*, **94,** 3007–3014.

Sutor, A.H., von Kries, R., Cornelissen, E.A., McNinch, A.W. & Andrew, M. (1999) Vitamin K deficiency bleeding (VKDB) in infancy. ISTH Pediatric/Perinatal Subcommittee. International Society on Thrombosis and Haemostasis. *Thrombosis and Haemostasis*, **81,** 456–461.

Telen, M.J. (2001) Principles and problems of transfusion in sickle cell disease. *Seminars in Hematology*, **38,** 315–323.

The Stationary Office (2002) *Guidelines for the Blood Transfusion Services in the United Kingdom*, 6th edn. The Stationary Office, UK.

United Kingdom Haemophilia Centre Directors' Organisation (1997) *Therapeutic Products to Treat Haemophilia and Other Hereditary Coagulation Disorders*. Available at http://www.medicine.ox.ac.uk/ohc/ukhcdo.htm.

Urban, A.E., Popov-Cenic, S., Noe, G. & Kulzer, R. (1984) Aprotinin in open-heart surgery of infants and children using the heart-lung machine. *Clinical Therapeutics*, **6,** 425–433.

Urlesberger, B., Zobel, G., Zenz, W., Kuttnig-Haim, M., Maurer, U., Reiterer, F., Riccabona, M., Dacar, D., Gallisti, S., Leschnik, B. & Muntean, W. (1996) Activation of the clotting system during

extracorporeal membrane oxygenation in term newborn infants. *Journal of Pediatrics*, **129,** 264–268.

Vichinsky, E., Haberkern, C.M., Neumayr, L., Earles, A.N., Black, D., Koshy, M., Pegelow, C., Abboud, M. & Ohene-Frempong, K. (1995) A comparison of conservative and aggressive transfusion regimens in the perioperative mangement of sickle cell disease. *New England Journal of Medicine*, **333,** 206–213.

Vichinsky, E.P., Luban, N.L., Wright, E., Olivieri, N., Driscoll, C., Pegelow, C.H. & Adams, R.J. (2001) Stroke prevention trial in sickle cell anemia: prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion*, **9,** 1086–1092.

Wandt, H., Frank, M., Ehninger, G., Schneider, C., Brack, N., Daoud, A., Fackler-Schwalbe, I., Fischer, J., Gackle, R., Geer, T., Harms, P., Loffler, B., Ohl, S., Otremba, B., Raab, M., Schonrock-Nabulsi, P., Strobel, G., Winter, R. & Link, H. (1998) Safety and cost effectiveness of a $10 \times 10(9)$/L trigger for prophylactic platelet transfusions compared with the traditional 20×10^9/L trigger: a prospective comparative trial in 105 patients with acute myeloid leukemia. *Blood*, **91,** 3601–3606.

Welch, C.R., Talbert, D.G., Warwick, R.M., Letsky, E.A. & Rodeck, C.H. (1995) Needle modifications for invasive fetal procedures. *Obstetrics and Gynecology*, **85,** 113–117.

Williamson, L.M. (1998) Transfusion-associated graft-versus-host-disease: new insights and a route towards therapy. *Transfusion Medicine*, **8,** 169–172.

Williamson, L.M. (2000) Leucocyte depletion and the blood supply – how will patients benefit? *British Journal of Haematology*, **110,** 256–272.

Williamson, L.M., Wimperis, J.Z., Wood, M.E. & Woodcock, B. (1996) Fludarabine treatment and transfusion-associated graft-versus-host-disease. *Lancet*, **348,** 472–473.

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