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Guidelines for administration of blood products: transfusion of infants and neonates

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Although the transfusion needs of infants command a relatively small proportion of routine blood bank workload, it is important to bear in mind that babies in special-care units are now amongst the most intensively transfused of all hospital patients. Despite such a high volume of activity, this area of transfusion practice is beset with uncertainties. Many widely accepted practices are not based on secure scientific foundations and could benefit from controlled investigation.

These guidelines seek to identify those practices which by broad agreement seem to be most firmly justified. The clinical indications for transfusion sometimes differ from those for adults, and neonates are more susceptible than adults to some of the various harmful effects of transfusion. As a consequence of the frequency of transfusion, the associated hazards are correspondingly increased. In practice, selection of blood products, compatibility testing and their administration also require separate consideration.

Detailed discussion of the clinical indications for transfusion of individual blood products are beyond the scope of the present guidelines and readers are referred to specialist publications. For the purpose of these guidelines neonates are considered to be babies within 4 weeks past their normal gestational age. Unless explicitly stated as applying to neonates, other recommendations have been considered in the context of transfusions within the first year of infant life.

RED CELL TRANSFUSION

For practical purposes, these are categorized according to the volumes administered as this has practical relevance to the specifications of product required. Most are small volumes given to replace the blood losses of investigative sampling or to alleviate the anaemia of prematurity. Larger transfusions will also be needed for replacement of surgical or pathological blood loss in common with adult transfusion practice. At the other extreme are exchanges or equivalent massive transfusions (e.g. during extra-corporeal membrane oxygenation, ECMO; or cardiac bypass surgery) during which in excess of the entire blood volume may be transfused.

It must be appreciated that the metabolic concerns governing the choice of blood only apply if substantial volumes of blood are to be given and are not relevant to top-up transfusions. Similarly, the freshness of blood in terms of its haemostatic qualities is of no relevance when only small volumes are given.

Source of blood for transfusion

Transfusion specialists in the U.K. agree that blood donated by unpaid volunteers selected and tested according to National Guidelines (UK BTS/NIBSC, 1993) fully meets safety requirements. Walking donor programmes, schemes entailing collection of small volumes of transfusable blood as and when required from special panels of donors, are vulnerable to both serological and viral transmission mishaps and can no longer be condoned. In addition, Medicines Control Agency regulations and Product Liability requirements mandate stringent standards for record keeping, blood grouping and microbiological screening which prove difficult to meet under the pressures of providing acute clinical services. Directed donations (including donations from relatives) cannot be assumed to be safer than microbiologically screened volunteer donations (see Table 1) and their use is not advocated. On

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Table 1. Microbiological screening of volunteer donor blood collected in the U.K.

Hepatitis B (HBsAg)
Hepatitis C (anti-HCV)
Human immunodeficiency virus types 1 and 2 (anti-HIV 1/2)
Syphilis
Cytomegalovirus (anti-CMV) for selected recipients

rare occasions the use of maternal blood may be permissible; however, fatal graft versus host disease (GVHD) has occurred in this situation and prior irradiation of blood is necessary (Vogelsang, 1990).

Pretransfusion testing (for neonates and infants within the first 4 months) (Table 2)

Samples from mother and neonate should be obtained and the ABO and RhD groups determined. The maternal serum should be screened for the presence of atypical antibodies and a direct antiglobulin test (DAT) done on the neonate's red cells.

If maternal blood is unavailable a neonatal sample should be screened to exclude atypical antibodies. The presence of these either in the maternal or neonatal serum or a positive DAT on neonatal red cells may reflect the presence of haemolytic disease of the newborn (HDNB). In such cases special serological procedures will be necessary to determine the infant's blood group and allow selection of appropriate blood for transfusion. Note the baby's ABO group is determined from the red cells alone since the corresponding antibodies will be weak or absent in the serum. The serum may contain passively transferred maternal antibodies.

The choice is between:

1 Use of the infant's own ABO group or, if necessary, an alternative compatible ABO group provided the above requirement is met.
2 If the mother's blood group is unknown, blood should be cross-matched using the indirect antiglobulin test against the baby's serum to ensure ABO compatibility.
3 Group O blood donations are generally suitable, but if used for massive transfusion to non-group O recipients these must be screened to exclude donations with high anti-A,B titres.

Note. In the absence of a direct matching policy for each transfusion episode (see next subsection) the use of donations other than group O requires total assurance in the systems for ABO designation of the intended recipient.

In practice, because of the other requirements of blood for neonatal use (described below), Transfusion Centres may specifically designate a supply of low anti-A,B titre group O RhD negative blood for use in neonatal transfusions (see Appendix 1).

Need for conventional 'cross-matching'. Provided that there are no atypical antibodies demonstrable in maternal/or infant's serum and the direct antiglobulin test on the infant's red cells is negative, a conventional cross-match is unnecessary. The Transfusion Centre may, however, recommend that the ABO/Rh group be confirmed on all blood transfused without direct cross-matching.

Small-volume replacement transfusions can be given repeatedly during the first 4 months of life without further serological testing. The formation of alloantibodies has been shown to be exceptionally rare during this period and appears to be related to repeated massive transfusions and the use of relatively fresh blood. It is only, therefore, under these circumstances that repeat antibody screening of the recipient is required.

Historically, practice has been to perform conventional cross-matching using maternal serum or, if unavailable, the infant's serum prior to each transfusion. This practice and, in particular, neonatal sampling for routine transfusions is now regarded as unnecessary.

If the antibody screen and/or DAT are positive, serological investigation and full compatibility testing will be necessary.

After the first 4 months of life compatibility testing should conform to the requirements for adults as described in BCSH Guidelines (BCSH, 1991).

Presentation of red-cell products

Small-volume transfusions. Primary packs containing either whole blood or red cells (haematocrit 0·55–0·75) with multiple aseptically sealable satellites are ideal. These enable transfusion of several small aliquots from a single donation.

Despite the extremely low risks of virus transmission by transfused blood in the U.K., every effort should be taken to minimize the number of donor exposures to which any infant is exposed. This can be done by dedication of a single donation for each patient as well as by ensuring that an adequate transfusion volume is administered on each occasion.

Exchange transfusions. Plasma-reduced red cells (within a haematocrit range of 0·50–0·60) are the most

Table 2. Pretransfusion testing of blood within the first 4 months

Maternal samples
1. ABO and RhD group
2. Antibody screen
Infant samples
3. ABO and RhD group
4. Direct antiglobulin test (DAT)
5. Antibody screen (if maternal sample uanvailable)

generally acceptable products for exchange transfusion. Where these are not routinely available, whole blood donations can be used but partial concentration by removal of around 120 ml of plasma into a sterile transfer pack may be necessary to provide an acceptable haematocrit. Red cells as conventionally provided concentrates (haematocrit 0·55–0·75) may be less satisfactory in that those packs with the highest haematocrit levels may require simultaneous administration of a plasma expansion material. This can be achieved with saline or 4·5% albumin. Fresh frozen plasma (FFP) has often been used for this purpose but it doubles the donor exposure risk and is therefore not recommended unless indicated as a product in its own right. For smaller transfusions, saline will normally be entirely satisfactory as a resuspension material.

Despite initial reservations regarding their suitability, red cells in optimal additive solutions, e.g. SAG-M (see Appendix 2), are increasingly used for top-up transfusion. There is so far no agreement regarding their suitability for exchange transfusions but there is concern that their use could lead to risks of metabolic, haemostatic and oncotic pressure problems.

Age of blood for transfusion

The age of blood does not matter for small-volume top-up transfusions and blood can be used at any time throughout its approved storage life.

It is a common misconception that fresh blood is necessary for all neonatal transfusions. In practice, the needs for the separate attributes of fresh blood require individual consideration bearing in mind the volume to be transfused. Supernatant plasma potassium can reach concentrations of up to 30 mmol l^{-1} in 5-week-old blood and this is the most important reason for limiting the age of red cells for neonatal transfusions. Blood for exchanges and other large transfusions should therefore ideally be used within 5 days of collection, i.e. 120 h from midnight of the day of collection (see Table 3). If this is not available, the red-cell pack may be concentrated by removal of the supernatant plasma and the transfusion volume restored with 4·5% albumin. The content of potassium is small in top-up transfusions in relation to daily needs and practice has shown that blood of any storage age is perfectly safe.

Table 3. Blood for neonatal exchange transfusion: considerations for selection

Product:	Plasma-reduced red cells (Hct 0·55–0·60)
Age:	Within 5 days of collection
Blood group:	ABO group of neonate, or an alternative provided that it is compatible with maternal ABO antibodies. Otherwise use designated group O Rh compatible units
Antibody screen:	Exclude high anti-A,B titres (group O donations) and other significant irregular blood-group antibodies
Compatibility:	Compatible with any maternal irregular antibodies
Anti-CMV status:	Negative if used for vulnerable recipients (see subsection on CMV infection)
Haemoglobin S Screen:*	Negative

* Advisable unless the Regional Transfusion Centre recommends that screening is unnecessary.

Storage-related depletion of 2,3 diphosphoglycerate (2,3 DPG) and the resulting high oxygen affinity is a theoretical disadvantage of aged blood, but there is no evidence that this constitutes a clinical problem. For top-up transfusions, the dilution effect renders the 2,3 DPG content of the donor blood immaterial. A number of studies show reasonable retention of 2,3 DPG levels (> 70%) and oxygen affinity during the first 5 days of storage—the most profound deterioration occurs after this time. 2,3 DPG also regenerates rapidly following transfusion. It seems reasonable, however, for exchange and other massive transfusions in the most critically ill neonates to use blood as close to the collection date as is conveniently possible provided that all microbiological testing requirements have been met.

The use of close-to-collection-date (24–48 h) donations for prevention of haemostatic problems during

massive transfusion of high-risk neonates has re-emerged as a contentious issue. In the presence of some supportive evidence (Manno *et al.*, 1991), a permissive policy seems reasonable for these rather uncommon transfusions pending availability of more conclusive evidence.

The use of absolutely 'fresh' blood (e.g. prior to required testing and release procedures) with the aim of contributing haemostatic and anti-infective factors is not acceptable. Diagnosis of the specific haemostatic lesion and appropriate therapy, e.g. platelet concentrates, cryoprecipitate or FFP, should be instituted.

Indications for top-up transfusions

As for any red-cell transfusion, reduction of the red-cell mass and its oxygen transport capacity to the extent that it prejudices cardiorespiratory function constitutes the fundamental indication for transfusion. Haemoglobin estimation alone permits an imperfect assessment, particularly within the neonatal period and is in any case complicated by the gestational age and prematurity associated changes. Haemoglobin reduction coupled with symptoms that are presumed consequences of anaemia at this time, for example feeding difficulties, lethargy and failure to thrive, are generally agreed to support a need for transfusion. It must be admitted, however, that controlled studies have not so far provided clear evidence of clinical benefit following transfusion under these circumstances. Nevertheless, haemoglobin concentrations provide the only practical guide in the absence of more sophisticated physiologically validated assessments of red-cell mass or oxygen availability.

It is suggested that transfusion should be considered for any symptomatic neonate whose haemoglobin concentration is less than 10·5 g dl^{-1}. It is generally accepted that neonates requiring supplemental oxygen should be maintained at a higher value. For example, target haemoglobin values of 13·0 g dl^{-1} have been suggested in the presence of severe pulmonary or cardiac disease.

When transfusion is given for the anaemia of prematurity, the volume transfused should be sufficient to increase the haemoglobin level to within the range of that found in full-term babies.

Blood sampling for investigation purposes is well recognized to contribute to neonatal anaemia, and replacement of these losses by transfusion is considered to be fully justified. This is the most frequent indication for transfusion in preterm infants although there is no common agreement about the frequency and volume of replacements required.

Rates and volumes for transfusion

Because of the risk of bacterial proliferation in non-refrigerated blood, transfusions from each blood pack should not exceed 5 h duration. Neonates are particularly vulnerable to circulatory overload, and transfusion rates must therefore be carefully controlled. Volumes of around 5 ml kg^{-1} h^{-1} are regarded as safe; infusion rates will need to be increased in the presence of active haemorrhage. Lower rates of transfusion should be selected when there is a risk of cardiac failure. If large volumes are transfused in a short space of time, diuretics should also be considered. Transfusions are most conveniently given via syringe pumps (provided a pressure warning device is incorporated). The syringe can be preloaded with blood from the pack, filling the syringe through a filter assembly. Larger volumes are best administered via standard blood administration sets incorporating a calibrated burette reservoir. The routine use of microaggregate filters during neonatal top-up transfusions has not been shown to be necessary. A reasonable approach which parallels their use in adult medicine would be to recommend filter use for massive transfusions (> one blood volume every 24 h) or where respiratory distress is present, although their benefits in these situations are still unproven.

Blood warmers

These should be used during rapid blood replacement, for example during exchange transfusions. Only approved and regularly maintained blood warming equipment should be used. Both fatal haemolytic transfusion reactions and bacteriological contamination have followed use of inappropriate blood warming procedures.

TREATMENT OF HYPOVOLAEMIC SHOCK/PLASMA VOLUME EXPANDERS

Albumin solutions, usually 4·5% in isotonic saline, are the preferred plasma volume expansion agents. Container volumes of 100 ml (4·5%) are available for paediatric use. FFP should not be used in these situations unless there are co-existing coagulation abnormalities.

Albumin solutions can be rapidly available as first-line treatment for unexpected hypotensive shock when the cause is unknown.

Exchange transfusion for polycythaemia

Hyperviscosity arising from polycythaemia (e.g. where the central venous haematocrit exceeds 0·65) can be

associated with significant morbidity. Serious pathology (renal vein thrombosis) can occur without warning symptoms. Partial exchange can be employed to reduce the haematocrit to 0·55 (Letsky, 1991). A 4·5% human albumin solution exchanged in 10-ml aliquots is the preferred material unless coagulation abnormalities indicate a need for FFP.

FRESH FROZEN PLASMA (FFP)

General recommendations for the use of FFP are available (BCSH, 1992a).

Disseminated intravascular coagulation (DIC) is one of the commonest coagulation problems. This may require FFP supplemented by cryoprecipitate if there is evidence of a severe consumptive state with fibrinogen depletion.

PLATELET THERAPY

General recommendations for the use of these products are available in the recently published guidelines (BCSH, 1992b). However, thrombocytopenia is believed to be more hazardous in neonates and prophylactic therapy is probably justified at counts below $30 \times 10^9\ l^{-1}$ or in the case of the very sick and premature when counts fall below $50 \times 10^9\ l^{-1}$. Thrombocytopenia may result from sepsis, or DIC, and may also be a complication of a variety of neonatal infective problems. Generally, one platelet concentrate will constitute a single dose—it will also contribute approximately 50 ml of 'fresh' plasma. If volume overload is a particular concern, the dose may be concentrated even further by arrangement with the Regional Blood Transfusion Centre. It is then necessary to allow the platelet packs to stand for about 1 h without disturbance before resuspension is possible. Platelets concentrated in this way must be administered within 12 h, as prolonged storage in this reduced volume is unsatisfactory.

Neonatal alloimmune thrombocytopenia

Specialist advice should be sought for the management of this condition. Emergency treatment of unexpected and symptomatic cases can usually be provided by transfusion of a unit of washed maternal platelets.

GRANULOCYTE THERAPY

The benefit of granulocytes in the management of neonatal sepsis has not been conclusively confirmed and treatment is best reserved for those serious cases in which antibiotic therapy alone appears insufficient. Treatment should not be contemplated without proven or strongly suspected bacterial sepsis coexisting with low blood neutrophil counts. A dose contributing around $0·5–1·0 \times 10^9$ granulocytes kg^{-1} is probably adequate. Treatment may be required twice daily for several days in succession. Granulocytes may be obtained by leukapheresis or from random donor buffy coats. Unless red cells are removed from buffy coats, compatibility selection must be as for red-cell administration. Granulocyte concentrates carry a risk of cytomegalovirus (CMV) transmission and CMV seronegative donations should be used where appropriate (see subsection below on CMV infection). Granulocyte concentrates must be irradiated where recipients are judged to be vulnerable to GVHD.

SPECIAL HAZARDS OF TRANSFUSION IN THE NEONATAL PERIOD

These problems are mainly confined to exchange transfusions or other circumstances of massive blood replacement.

Hypocalcaemia (total serum calcium $<1·5$ mmol l^{-1}, ionized calcium $<0·8$ mmol l^{-1}). Neonates are more likely than adults to develop hypocalcaemia although the clinical effects may be less pronounced. This complication is now rare following the use of citrate phosphate dextrose in place of acid citrate dextrose as an anticoagulant but it can follow rapid transfusion as, for example, during exchanges. Blood should be warmed to minimize the effect and if clinical suspicion of hypocalcaemia is confirmed biochemically, calcium gluconate should be administered.

Citrate toxicity can be a problem for premature infants and shows as an alkalosis with increased plasma bicarbonate.

Rebound hypoglycaemia can be induced by the high glucose levels of blood transfusion anticoagulants. Blood glucose levels should be monitored during and following exchange transfusions.

Thrombocytopenia can be a problem following exchange transfusion and may reflect either a dilution effect or an underlying process of DIC.

Graft versus host disease (GVHD) has been an exceptionally rare problem of intrauterine transfusions and neonatal transfusions. The actual level of risk is unknown and there is controversy over the need for prophylactic irradiation of cellular blood components. Infants with congenital cellular immune deficiency should certainly be given blood components

which have been irradiated. For other patients the most persuasive evidence supports the use of irradiation for intrauterine transfusion, any subsequent exchanges such babies may receive and for exchanges given to very low birth-weight babies (< 1500 g). Irradiation is also necessary for directed blood donations from first-degree relatives in view of the propensity for shared haplotype transfusions to induce GVHD. Doses of 25 Gy are used. Because of the accelerated K^+ leak, irradiated red cells should be used within 4 days for top-up transfusions and 24 h for exchange transfusions.

Cytomegalovirus infection. Anti-CMV negative cellular components should be given to very low birth-weight babies (< 1500 g) as it is only in this category that significant morbidity occurs. If these are unavailable, leucocyte depletion of blood components by filtration is believed to be effective.

Transfusion overload. Neonates are particularly susceptible to volume overload and accordingly need careful monitoring.

Haemolytic transfusion reactions in necrotizing enterocolitis. These rare but serious events are due to destruction of T-activated autologous red cells by the natural anti-T in transfused plasma. The transfusion laboratory should be notified to enable the diagnosis of T-activation to be investigated if this condition is suspected in infants who require transfusion. If confirmed, transfusion of any product containing plasma must be avoided.

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APPENDIX I

Additional serological screening of blood for neonatal use (recommendations pertaining to blood likely to be used for massive/exchange transfusions)

1. *Exclusion of group O donations with high levels of anti-A,B.* In the U.K., it is not mandatory to screen all group O donations for the presence of high levels of anti-A,B. However, additional testing is recommended on group O donations used for massive/exchange transfusion of neonates to exclude blood containing high-titre anti-A,B. This policy will ensure protection for non-group O neonates receiving large-volume group O transfusions.

There is no general agreement on measures for routine screening for significant titres of haemolysis or agglutinins. Exclusion of donations with saline titres of >32 or examination of a 1:50 dilution of donor plasma against A1 and B cells by indirect antiglobulin test are acceptable approaches.

2. *Screening for irregular blood-group antibodies.* Donation screening protocols for irregular blood-group antibodies acceptable for routine adult transfusion purposes may not be adequate for massive neonatal transfusions.

Under these circumstances it is recommended that donor plasma be screened fully for all common clinically significant antibodies as is customary for transfusion recipients. The same caution applies when equivalent volumes of FFP are transfused to neonates.

APPENDIX II

Composition of saline adenine glucose/SAG-M (Baxter) optimal additive solution

		Estimated toxic level for neonates (Luban *et al.*, 1991)
Volume	100 ml	
Sodium chloride	877 mg (150 mEq l^{-1})	
Dextrose	818 mg	240 mg kg^{-1} day^{-1}
Mannitol	525 mg	360 mg kg^{-1} day^{-1}
Adenine	16·9 mg	15 mg kg^{-1} $dose^{-1}$

This solution is in common use within the U.K.

Other formulations of optimal additive solutions are available, some of which contain substantially greater dextrose concentrations to enable better red-cell preservation, and these cannot be assumed to be equally suitable for neonatal use without individual verification.