Guidelines for the administration of blood products

Earlier this year a document setting out guidelines for the administration of blood products to infants and neonates was published under the authorship of a working party of the British Committee for Standards in Haematology (BCSH) Blood Transfusion Task Force. These guidelines are the first of their type to be produced in the UK and are to be welcomed. Unfortunately their publication in a specialist transfusion journal has probably meant that they may not have reached a wider paediatric audience.

The authors acknowledge that many accepted practices are not founded wholly on objective investigation. We are uneasy about ‘broad agreement’ as a basis for firm recommendations. Many would view consensus medicine as a reduction to the lowest common denominator and one which stifles leading edge changes in practice. We believe that a set of guidelines should draw attention to evidence based recommendations but that an important additional role is to highlight uncertainties.

Evidence based recommendations

In these guidelines some very useful, clear statements are made, with well referenced substantiating evidence. These include widely accepted views such as that walking donor panels are no longer considered appropriate as a source of blood for neonatal transfusions. Others are based on sound evidence but are less widely appreciated, such as that red cell components may safely be used to the end of their full shelf life for small volume neonatal transfusions. Similarly, the use of satellite packs is an effective means by which to reduce donor exposure in extremely preterm neonates but only if the hospital transfusion laboratory uses them appropriately to the end of their shelf life and ensures the allocation of units to particular infants. The guidelines set out a clear pretransfusion testing protocol for neonates. This includes an indirect antiglobulin test to exclude atypical antibodies, and emphasises that further screening for red cell antibodies is unnecessary for the first four months after birth. This deserves wide publicity in service laboratories, particularly to those providing on-call services to neonatal units.

Red cell transfusion

The guidelines also briefly review the indications for red cell transfusions, a contentious area, on which there is an extensive literature. However, no mention is made of the use of erythropoietin, which may change transfusion requirements. The reader is referred to a recent review of the subject by Luban. Some uncertainties might have merited more critical discussion. Two prospective studies describe the inability of infants to develop alloantibodies,6 7 and this provides the justification for advising that repeat red cell antibody screening is unnecessary for four months. However, what is the effect of preterm birth on the ability to react to allogeneic red cell antigens? Is the ‘first 4 months of age’ the same in immunological terms for an infant born at 24 weeks as for one born at 36 weeks? Is there any evidence that birth matures the ability to form red cell alloantibodies and what are the effects of fetal transfusion on the alloimmune process?

Intrauterine transfusion

It might have been appropriate to have extended the initial brief, to include transfusion of the fetus. In many ways the conceptual division between the fetus and neonate is artificial. Immunological naïvety, the ability, or the inability, to react to an alloimmune stimulus, susceptibility to viral infections, and potentially long post-transfusion survival, are shared by both groups of patients. Delayed side effects relating to intrauterine transfusion may be dealt with by neonatal paediatricians and may include suppression of erythropoiesis, transfusion transmitted infection, possible induction of immune tolerance, and transfusion associated graft versus host disease (TA-GVHD).

Graft versus host disease

The risk of TA-GVHD in fetal and neonatal transfusion practice is small but finite and may be associated with immune naïvety and the proportionately large, fresh transfusions containing viable lymphocytes that these tiny patients may receive. There are very few reported cases of neonatal TA-GVHD and this may reflect its rarity, under
reporting, or the already established practice of gamma irradiation which is the only effective method of prevention of this virtually uniformly fatal complication of transfusion. There is definitely a need to irradiate all related directed donations and donations to infants with suspected or proved cellular immune deficiency. Other indications are more contentious. The guidelines suggest the use of irradiated products for intrauterine transfusions, any subsequent exchange transfusions such babies may receive, and exchange transfusions in very low birthweight babies. TA-GVHD after unrelated donor intrauterine transfusion alone has been described in only a single, controversial case report. It is unknown whether an intrauterine transfusion result in immunosuppression of the fetus leading to increased susceptibility to future TA-GVHD. The evidence appears to rest on four reported cases of an unrelated donation leading to TA-GVHD after exchange transfusion in immunologically normal neonates who had previously received intrauterine transfusions. Of these four cases, three were shown to be due to engraftment of lymphocytes from the exchange transfusion donor, which suggests a possible previous immunosuppressive effect of the intrauterine transfusion. The fourth case of TA-GVHD appeared to be due to one of the donors whose blood was used twice for intrauterine transfusion. There have also been five reported cases of TA-GVHD after exchange transfusion alone. Three occurred in preterm infants and two were at term. One case was described in Israel where the population is relatively homogenous, which may have increased the chance of an HLA match between donor and recipient. These cases of TA-GVHD must be viewed in the context of the thousands of exchange transfusions that have been performed. It therefore seems questionable to recommend irradiation of blood for exchange transfusion in very low birthweight babies, particularly as an effect of irradiation is to increase potassium egress from red cells.

Irradiated blood products
Gamma irradiation produces an increase in potassium egress from the red cells into the supernatant, which varies with the red cell concentration, the age of the red cells at the time of irradiation, and subsequent storage time. The potassium rise in the supernatant over the initial few days is greatest, falling away to approximately double the level in the non-irradiated counterpart for red cells in optimal additive solution component commonly used for top up transfusions. For red cells concentrated to a packed cell volume of 0.9, as may be used in fetal transfusions, the initial rise is steeper. However, as the guidelines rightly acknowledge, the total potassium content of a small volume transfusion is small and blood used for top-up transfusion should therefore be used to the end of its shelf life. The authors go on to recommend that irradiated red cells should be used within four days of storage. However, unpublished data from the North London Blood Transfusion Centre shows that at four days, irradiated red cell units in optimal additive solution, as often used in top up transfusions, only contains 3 mmol of potassium compared with 1 mmol per unit in the unirradiated counterpart. The neonatal guidelines also recommend that unirradiated blood for exchanges and other large transfusions should be used within five days of collection but that irradiated blood should be used within 24 hours. This may be overly cautious. Further unpublished data from the North London Blood Transfusion Centre shows that the total potassium content per unit of irradiated whole blood is only 4.2 mmol by day 4, compared with 2 mmol per unirradiated unit.

Filtration
The place of filtration might have usefully been clarified, particularly for a non-specialist readership. Microaggregate filters have not been shown to be beneficial in small volume transfusions for neonatal subjects. It is recommended that large volume transfusions and transfusions to critically ill infants should be filtered, although evidence of benefit is lacking. Filtration may also be used for leucodepletion. Increasingly leucodepletion is being performed by transfusion centres before issuing blood products rather than at the bedside. There is now evidence that multiply transfused infants below 36 weeks can, transiently, develop anti-HLA antibodies after as few as three transfusions. The clinical long term relevance of these antibodies is not known, nor of the immunological effects and induction of tolerance of repeated antigen loads and multiple transfusions from the same donor, as occurs with the use of multiple satellite packs. Leucodepletion may prevent some of these immunological effects of transfusion as well as the transmission of white cell associated organisms such as human T cell leukaemia virus and cytomegalovirus. However, filters are not yet capable of reducing the while cell content of components enough to prevent TA-GVHD. Further study of leucodepletion of components for neonatal transfusion should be encouraged.

Current clinical practices
FEAR OF TRANSFUSION OVERLOAD
Regrettably certain widespread, but unjustified practices in neonatal medicine are uncritically reinforced. In the UK it appears to be a common practice to follow transfusions of packed red blood cells in neonates with an injection of frusemide. However, there are no reported cases of overload in electively transfused preterm babies. Atrial natriuretic peptide release is triggered by vascular overload and no increase was demonstrated when preterm infants were transfused slowly with 10 ml/kg of packed red cells. In severe, chronic, euvoalaeamic anaemia, as may occur for example after chronic fetomaternal or twin to twin transfusion, a partial exchange transfusion with a red cell concentrate may be advisable rather than a top-up transfusion with frusemide cover. Present day practice is for top-up transfusions to consist of red cell concentrates with an adjusted packed cell volume ideally to 0.5—0.7. Polycythaemia, rather than volume overload, after red cell transfusion, may be a greater hazard in the newborn. The problem when excessively plasma reduced preparations are used inappropriately for exchange transfusions, there may be wider implications such as an increased risk of necrotising enterocolitis. It is conceivable that an increase in blood viscosity may further impair perfusion in already compromised bowel.

A single dose of frusemide leads to a substantial increase in sodium excretion. Many preterm babies are in precarious sodium balance and chronic sodium depletion is an important cause of growth failure. Frusemide is also a potent diuretic agent and repeated doses will contribute to the development of osteopenia of prematurity and nephrocalcinosis. Ductal patency, through the effect on renal prostaglandin E2 production, and ototoxicity are other potential hazards of frusemide use.

The majority of newborn babies receiving top-up red cell transfusions are not in heart failure. The situation may, however, be different from infants with bronchopulmonary dysplasia, in whom heart failure is not uncommon, although published data, supporting the use of diuretics, are not convincing. In the case of transfusions in infants with overt heart failure the logical approach would be to reduce the rate of transfusion to 2 ml/kg/hour.
FRESH FROZEN PLASMA OR HUMAN ALBUMIN SOLUTION

A further area of controversy in neonatal practice concerns the indications for the use of fresh frozen plasma. Both fresh frozen plasma and human albumin solution are widely used in neonatal intensive care units. It is accepted that fresh frozen plasma is not a suitable product for volume expansion in adults or children, but there are some grounds for questioning the extrapolation to extremely immature neonates. The need for volume expansion often occurs in babies who are septic and may also have a coagulopathy. The diagnosis of both these conditions is often difficult. If volume expansion is necessary it should be carried out without delay. Fresh frozen plasma, unlike human albumin solution, contains coagulation factors and the naturally occurring anticoagulant factors, as well as opsonins, and there is evidence that fresh frozen plasma may enhance neonatal neutrophil chemotaxis. However, while the manufacture of human albumin solution carries viral inactivation steps, viral transmission by fresh frozen plasma poses a small but finite risk. There is an urgent need for scientific study of the possible benefits of these two agents and comparison with other colloids. Moves to increase the microbiological safety of fresh frozen plasma include viral inactivation and the use of plasma from well characterised donors.

IMMUNOTHERAPY

The section on granulocyte treatment has suffered from oversimplification. Though there appears to be some evidence of benefit (though not from random donor buffy coat!), the practical and technical problems of transferring granulocytes from donor to patient quickly, effectively and repeatedly, make it beyond the reach of all but a few neonatal centres. The availability of the recombinant cytokines, granulocyte and granulocyte-monocyte colony stimulating factor may circumvent these problems and open up exciting possibilities for the enhancement of neonatal immune functions.

Register of rare conditions

A number of rare, but serious side effects of transfusion and errors in transfusion practice may be recognised by paediatricians. Examples include the incidence of cytomegalovirus pneumonitis in preterm infants, TA-GVHD, the incidence of T activation and problems of hyperkalaemia in infants undergoing large volume transfusions, particularly with irradiated red cell products. Similarly, rare disorders such as alloimmune neonatal thrombocytopenia may be better recognised and appropriately managed if awareness is increased by inclusion in a reporting system. The medical director of the National Blood Authority, or the British Paediatric Surveillance Unit would be appropriate bodies to collate such data and to utilise it to best effect.

Future guidelines

Any set of guidelines needs regular revision. The outcomes of current clinical trials evaluating the use of growth factors, immunological enhancement treatments, and the use of specific blood components for neonatal use, are likely to change neonatal transfusion practices over the next few years. We look forward to future updates from the British Committee for Standards in Haematology Blood Transfusion Task Force.
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