FETAL AND NEONATAL TRANSFUSION

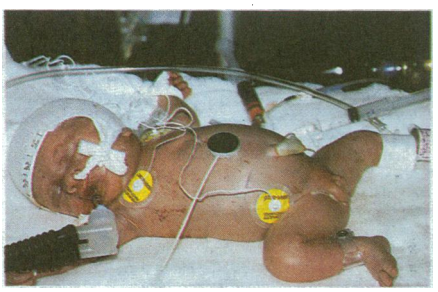
Elizabeth A Letsky

Ill babies are more likely to be transfused than any other patients

The special care baby unit presents unique problems for the physician caring for ill, newborn infants. These infants, both mature and preterm, are more likely to be transfused with blood products than any other group of patients.

The indications for tranfusion and the techniques used by the blood bank to provide for these needs have changed appreciably during recent years.

Exchange transfusion



Exchange transfusion for haemolytic disease of the newborn in a white baby of 31 weeks' gestation. Pigmentation caused by phototherapy. Haemoglobin concentration was 38 g/l at delivery and three double volume exchanges were carried out. Infant now well and 6 years old.

Causes of jaundice during first week of life

- Haemolysis
- Infections
- Polycythaemia
- Metabolic disorders
- Neonatal hepatitis
- Increased enterohepatic absorption
- Enclosed haemorrhage
- Miscellaneous disorders

The main indication for exchange transfusion in the neonate in the United Kingdom is to prevent the kernicterus caused by a rapidly rising bilirubin concentration. Newborn infants, particularly those born prematurely, are susceptible to the dangers of hyperbilirubinaemia mainly because of the inability of the immature liver to deal with the breakdown products of haemoglobin. Any extra haematological stress can result in a further increase in the bilirubin concentration and the development of kernicterus unless treated promptly.

There are many cases of neonatal jaundice, but the most common and clinically important is haemolytic disease of the newborn. In recent years the rate of exchange transfusion for hyperbilirubinaemia has decreased, mainly for three reasons:

(1) Since the introduction of immunoprophylaxis with anti-Rh immunoglobulin, the number of cases of haemolytic disease has fallen considerably (see *Haemolytic disease of the newborn and its prevention*).

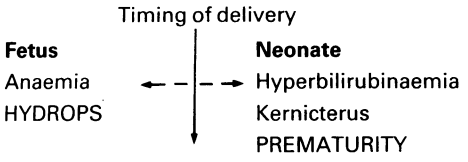
(2) Successful intrauterine correction of anaemia is now carried out before delivery by transfusing red cells that are not affected by the mother's immune antibody.

(3) Other methods of preventing kernicterus, such as intensive phototherapy after delivery, are now used successfully.

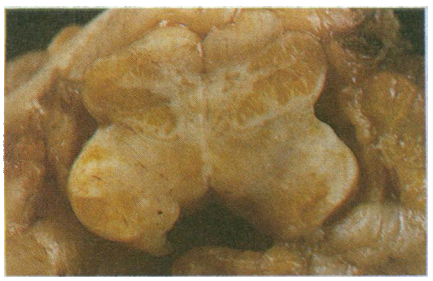
Intrauterine transfusions to correct fetal anaemia

Assessment of the fetus at risk is made from the history, quantitation of the mother's antibodies, the bilirubin concentration of amniotic fluid and, ultimately, fetal blood sampling.

Fetal blood sampling and intrauterine transfusion can be carried out as early as 18 weeks' gestation. Seriously affected fetuses may receive a series of tranfusions at two to four week intervals, depending on the rate of fall of the haemoglobin concentration and the need to prevent or revert hydrops. Group O red cells carrying blood group antigens that do not react with the maternal antibody are used, with a packed cell volume of about 0·70 to achieve the minimum total volume load and the maximal correction of anaemia. Transfusions are given intravascularly (for immediate correction) and these may be combined with intraperitoneal administration (when



Problems in haemolytic disease of the newborn.



Necropsy specimen of medulla of brain from an infant who died of kernicterus caused by haemolytic disease of the newborn. Note staining of vital areas of brain tissue with bilirubin.

Reasons for fall in rate of exchange transfusion

- Decrease in number of cases of severe haemolytic disease since introduction of prophylaxis with anti-D globulin
- Introduction of successful intrauterine treatment
- Success of other methods of preventing kernicterus—for example, phototherapy

Possible complications of exchange transfusion

- Hyperglycaemia
- Hyperkalaemia
- Hypocalcaemia
- Hypovolaemia
- Hypothermia
- Air embolism
- Thrombocytopenia
- Coagulation factor deficiency
- Haemolysis
- Alloimmunisation
- Graft versus host disease

blood is slowly absorbed through the lymphatics); this combination increases the interval between transfusions by maintaining adequate haemoglobin concentrations for longer. The blood should be less than 72 hours old and negative for cytomegalovirus; ideally, it should be irradiated to prevent graft versus host disease. As a result fetuses with severe, but treated, haemolytic disease may be born at 36 weeks' gestation or more with a negative direct antiglobulin (Coombs) test and do not develop pathological jaundice. They may only require "top up" transfusions during the first few weeks of life.

Haemolytic disease of the newborn caused by antibodies other than anti-D

After anti-D antibody, anti-c and anti-Kell are next in importance. Haemolytic disease as a result of anti-c may be severe enough to cause fetal hydrops if appropriate measures are not taken. That caused by anti-Kell is rare but can be severe and rapidly fatal early in gestation. The criteria for its assessment are somewhat different from those for haemolytic disease caused by anti-D, because it is thought that the antibody causes suppression of erythropoiesis in the fetus rather than just red cell destruction. As a consequence, the bilirubin concentration in the amniotic fluid may be low in relation to the severity of the anaemia. Management should comprise early fetal blood sampling and Kell grouping and regular ultrasonography if immediate transfusion is not indicated.

ABO incompatibility

The chance of ABO incompatibility is 1:5, but severe ABO haemolytic disease occurs in only about 1:3000 births. Mild disease occurs in about 1:150 births. Less than 5% of affected babies need phototherapy and only rarely is exchange transfusion required.

The diagnosis of ABO haemolytic disease is usually made in mature infants who are not anaemic and who develop jaundice during the first 24 hours of life. Characteristically the blood film contains large numbers of spherocytes, the mother is group O with IgG anti-A or anti-B antibodies (lysins), and the baby's blood group is A or B. The direct antiglobulin test may be negative or weakly positive. These infants can develop jaundice severe enough to lead to kernicterus.

It is particularly important to be aware of the possibility of ABO incompatibility, because as early discharge from maternity units becomes more common, healthy mature babies can develop dangerous concentrations of bilirubin at home. If phototherapy does not control the jaundice exchange transfusion with group O red cells—ideally suspended in group AB plasma—will be necessary.

Complications associated with exchange transfusions

Mortality from treatment with blood components in neonates is low, and most transfusion related deaths are associated with exchange transfusions.

- *Metabolic complications* that have been reported both during and after transfusion are broadly similar to those encountered in adults. They include *hypoglycaemia* (which is exaggerated in preterm infants who are hypoglycaemic to start with), *hyperkalaemia,* and *hypocalcaemia.*
- *Cardiac and vascular complications* may also occur; careful monitoring of input and output during exchange is mandatory to avoid acute hypervolaemia, and aliquots of 5-10 ml should be used. There is no point in carrying out more than a double volume exchange, as this will remove the maximum bilirubin and replace most of the sensitised red cells with cells unaffected by the maternally derived antibody.
- *Hypothermia* as a result of not warming the blood properly may cause fatal cardiac arrhythmia.
- *Air embolism* has been reported during exchange transfusion. This is caused by negative pressure occurring in the umbilical vein that results in air entering the exchange transfusion system. Exchange transfusion should always be carried out through the umbilical vein taking care not to damage vessels. The packed cell volume of transfused blood should be no more than 0·50 to avoid hyperviscosity, as the portal vein may thrombose leading to portal hypertension and varices in the second year of life. The umbilical artery should be avoided, as spasm can lead to ischaemia of the lumbar spinal cord and paralysis of the lower limbs.

Changing pattern of transfusion in the newborn

Exchange transfusion

Hyperbilirubinaemia

(Respiratory distress syndrome)

(Disseminated intravascular coagulation)

Partial exchange

Polycythaemia

Albumin

Volume expander in neonates in shock

"Top up" (preterm infant)

Red cells—anaemia

Fresh frozen plasma—coagulopathy and disseminated intravascular coagulation

Platelets—thrombocytopenia

Granulocytes—infection

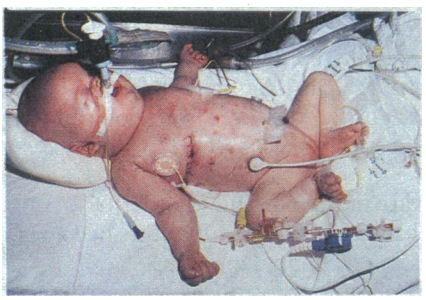
- *Haemostatic complications* (thrombocytopenia and coagulation factor deficiency) may result because stored blood lacks viable platelets and the labile clotting factors V and VIII.

- *Haemolysis* may be caused by forcing red cells through a fine bore needle or catheter, or by excessive heating in a blood warmer.

- *Alloimmunisation*—It is probably not necessary to continue crossmatching red cells for repeated transfusions because neonates do not readily form alloantibodies. The first crossmatch should be carried out against maternal serum.

- *Graft versus host disease* in neonates takes the form of skin rash, hepatitis, and marrow aplasia. It is rare, but it may be an important cause of death after exchange transfusion and can be prevented by irradiation of the blood before infusion into the fetus or preterm infant.

Partial exchange transfusion and polycythaemia



Infant with superior vena cava thrombosis associated with polycythaemia and catheterisation.

Practical approach to diagnosis and treatment of polycythaemia

- Healthy infants born at full term are at little risk and need not be screened.
- Paediatricians must be constantly alert to early clinical signs.
- Babies with mild symptoms of hyperviscosity should be kept warm and well hydrated to prevent sludging.
- Babies with serious symptoms should have partial exchange transfusion with fresh frozen plasma to bring packed cell volume down to 0·55 (20 ml/kg).

Polycythaemia and hyperviscosity are not synonymous, but the most important dependent variable affecting whole blood viscosity in neonates is the packed cell volume. There is an almost linear relation between viscosity and packed cell volume below 0·60-0·65, but the relation becomes exponential when the packed cell volume is any higher.

The reported incidence of neonatal "thick blood syndrome" varies considerably depending on the criteria used for diagnosis, but a venous packed cell volume of 0·65 or more is the generally accepted screening test. The overall incidence is said to vary between 4% and 0·45%. The types can be divided into two groups, active and passive. The active form occurs when the fetus produces an increased number of red cells in response to intrauterine hypoxia and other stimuli, and the passive form when the fetus receives a red cell transfusion. This may be maternal, twin to twin, or the result of delayed clamping of the cord.

In normal infants born at full term the most common cause is delayed clamping of the cord. Morbidity and mortality in fetus to fetus transfusion are at least as high in the polycythaemic recipient as in the anaemic donor twin.

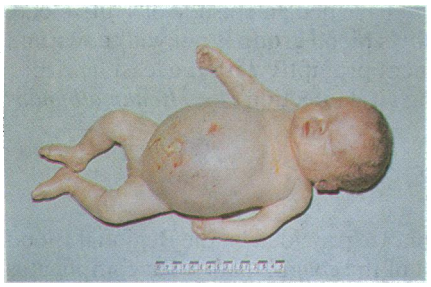
Clinical findings and management

Babies present during the first 24 hours when the packed cell volume rises as a result of a physiological decrease in plasma volume. The most consistent findings are lethargy and hypotonia within six hours after birth, poor sucking and vomiting, difficulty in arousal, irritability when aroused, poor response to light, tremulousness, and being easily startled. Some of these may be the result of the metabolic abnormalities commonly associated with polycythaemia rather than the direct result of the hyperviscosity itself. Complications include hyperbilirubinaemia with kernicterus and heart failure, as well as other problems of vascular occlusion. Respiratory distress and cyanosis together with congestive cardiac failure may be severe enough to simulate cyanotic congenital heart disease.

Sludging and formation of thrombi in the peripheral circulation can lead to tissue anoxia wherever the circulation is compromised. Seizures, priapism and testicular infarction, renal vein thrombosis, renal failure, gangrene, distal bowel obstruction, and necrotising enterocolitis have all been described. There may be appreciable neurodevelopmental abnormalities.

All infants with symptoms and hyperviscosity require treatment to relieve the immediate symptoms and prevent long term consequences. The aim is then to lower the packed cell volume and thereby the viscosity. Partial exchange transfusion is carried out, removing whole blood and replacing it with equal volumes of fresh frozen plasma to achieve a packed cell volume of 0·55, which is considered to be "safe".

Anaemia of prematurity



Neonatal death from hydrops in infant of 31 weeks' gestation. Unsuccessful attempts had been made to treat anaemia with intraperitoneal transfusions. Puncture marks are visible. Some of the ascites are undoubtedly unabsorbed transfused blood.

Infants with cardiac or pulmonary disease causing reduced arterial oxygen saturation may need to have haemoglobin concentration maintained between 160-170 g/l.

In recent years the survival of extremely small infants has improved, and those that are anaemic benefit from transfusion. It is essential to compare the actual concentration of haemoglobin with the expected concentration in a premature infant of similar birth weight and age. An important cause of anaemia is iatrogenic blood letting.

The haemoglobin concentration falls on average by 10 g/l/week from the second to the eighth week of life. It may fall naturally during this time to 70 g/l, and in an otherwise healthy premature infant this should cause no concern. A blood transfusion given solely on the basis of haemoglobin concentration is likely to be one of a series; the first will increase the concentration of haemoglobin A, shift the oxygen dissociation curve, and increase delivery of oxygen to the tissues. This will then depress production of red cells, and the concentration will fall even more before erythropoiesis is reactivated by tissue anoxia.

An important indication for transfusion is failure to achieve the expected daily weight gain. Regular transfusion in premature infants will result in improved weight gain among those who are lagging behind the expected average weight.

Clinical anaemia can be associated with a haemoglobin concentration as high as 105 g/l, emphasising that that measurement alone is no indication for giving or withholding transfusion. The physician will therefore have to make the decision using clinical judgment. A few simple guidelines should be instituted that will result in only essential transfusions being given:

(1) Record carefully all blood taken, and if 5-10% of the blood volume is removed over a short time replace by packed red cells.

(2) Measure haemoglobin concentration regularly.

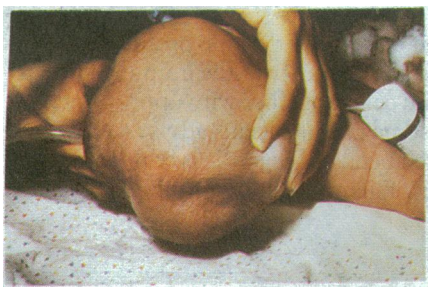
(3) Do not transfuse because of haemoglobin concentration alone.

(4) Evaluate weight gain, fatigue while feeding, tachypnoea, tachycardia, and hypoxia.

(5) Remember that infants with cardiac or pulmonary disease that is reducing the arterial oxygen saturation may need to have the haemoglobin concentration maintained in the range 160-170 g/l to ensure sufficient differential between arterial and venous oxygen tensions.

Complications of blood transfusion in premature neonates

In addition to those metabolic and haemodynamic complications that were described in association with exchange transfusion, there are some special complications that arise because of the neonate's immaturity, such as graft versus host disease and transmission of infection.



Oedema of the scalp in a baby with thrombosis of superior vena cava associated with polycythaemia and catheterisation.

Damage to vessel walls and hypercoagulable blood may lead to thrombosis of vessel

Transmission of infection (see *Infectious complications of transfusion*)

Post-transfusion hepatitis is probably the most common and serious problem associated with transfusion of blood and blood products. In neonates the risks of becoming a chronic carrier are increased.

Congenital cytomegalovirus infection has been reported in more than 3% of the offspring of seroimmune women, but it seems that infants born to mothers who are negative for cytomegalovirus are more prone to morbidity induced by neonatal cytomegalovirus infection. In healthy immunocompetent subjects, post-transfusion cytomegalovirus infection results in seroconversion with little or no morbidity except possibly a transient atypical mononuclear cell syndrome.

Problems associated with catheterisation of vessels

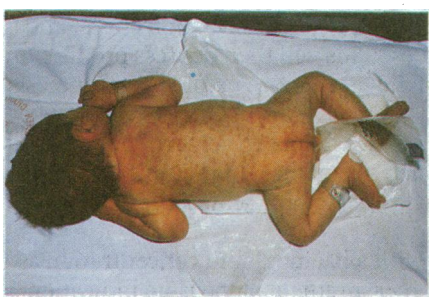
Damage to vessel walls and the hypercoagulable state in the newborn infant may lead to thrombosis of the vessel concerned.

Problems associated with provision of small aliquots of blood

Volumes of blood required in the nursery (other than for exchange transfusion) vary between 20 and 100 ml/transfusion. The usual single unit of freshly donated blood contains 450 ml, and if one is used to "top up" transfusions three quarters will be wasted. Procedures must be developed to provide unusually small quantities of reasonably fresh blood for transfusion to infants with minimum wastage.

Treatment with blood components

Albumin carries no risk of transmitting viral infection



Infant born at full term with alloimmune thrombocytopenic purpura.

Screening of infants at risk of hyperviscosity

- Screen those infants:
  - Who are small or large for gestational age
  - Who have diabetic mothers
  - Whose mothers had pre-eclampsia
  - Who have placental insufficiency syndrome
  - Who are twins
- Delay sampling until eight hours after delivery
- If capillary packed cell volume >0·65 to 0·70 venous packed cell volume should be checked

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Albumin

Human albumin 4·5% is often used in the delivery room to resuscitate neonates in shock who are presumed to have had an episode of acute blood loss. Its use is justified because the baby's blood group is not yet known and it is necessary to give optimum treatment promptly with the least hazard; albumin carries no risk of transmitting viral infection (see *Human albumin solutions*).

Fresh frozen plasma

Aliquots of 50 ml fresh frozen plasma are provided by the Regional Blood Transfusion Service for the treatment of the coagulopathy that complicates many neonatal conditions. These contain all the procoagulation factors (including V and VIII) that deteriorate during storage as well as naturally occurring anticoagulants, immunoglobulins, and albumin.

Platelets and granulocytes (see *Platelet and granulocyte transfusion*)

- *Platelets*—The most common cause of thrombocytopenia in the newborn is disseminated intravascular coagulation associated with infection. One unit of platelet concentrate is usually enough to treat any thrombocytopenic condition, and the volume can be reduced further if necessary.

Immune thrombocytopenia needs special consideration. Maternal IgG antiplatelet antibody crosses the placenta and can cause thrombocytopenia in the fetus and neonate. Spontaneous haemorrhage does not occur in the fetus. The main danger is a traumatic delivery, and if it is known that the fetus is—or may be—thrombocytopenic elective caesarean section may be planned. Platelet transfusion is of limited value, but high doses of IgG given intravenously to the mother before delivery or to the neonate after birth will usually cause an increase in the number of circulating platelets.

Alloimmune neonatal thrombocytopenia, which is analogous to haemolytic disease of the newborn, is caused by the formation by the mother of antibodies to a platelet antigen that the fetus has inherited from the father; the specificity of the antibody is almost always anti-PI^{A1}. The antibody (IgG) crosses the placenta and causes profound thrombocytopenia in the fetus. Mortality is about 14% (mainly caused by intracranial haemorrhage), and those who survive may be severely disabled. In fetuses known to be at risk early fetal blood sampling to estimate the platelet count should be carried out and weekly transfusions of PI (A1 negative) platelets given as indicated until the fetus is mature enough to be delivered. In an emergency or if the platelet antibody has not been identified washed maternal platelets can be used.

- *Granulocytes*—Severely infected neonates may develop profound neutropenia and because of the general immaturity of the immune system may benefit from transfusions of white cells, together with appropriate antibiotics. In the United Kingdom some paediatricians advise routine granulocyte transfusions in ill, infected neonates regardless of the white cell count in view of the impaired function of neutrophils in the neonatal period.

ANY QUESTIONS

Does resistance to giardiasis occur and if so by what mechanism?

Several observations, including the low rate of symptomatic disease in long term residents of an endemic area compared with short term visitors,[1] suggest that at least partial protective immunity leading to a degree of resistance may develop to *Giardia lamblia*. Probably, however, development of immunity requires long term exposure to the infection. The components of immunity are both cellular and humoral.[2,3] The latter is mediated through a systemic antibody and a specific local antigiardia secretory IgA response. The value of this is illustrated by the increased susceptibility to giardiasis of patients with X linked hypogammaglobulinaemia, common variable immunodeficiency, and selective IgA deficiency. The cellular response is thought to be important in the coordination of antibody production and in engaging specific antigiardia cytotoxicity. Its importance is illustrated by the failure of patients with AIDS to mount an adequate immune response to the parasite.—P NATHWANI, *registrar in infectious diseases, Glasgow*

1 Istre GP, Dunlop TS, Gaspard GB, *et al*. Waterborne giardiasis at a mountain resort: evidence for acquired immunity. *Am J Public Health* 1984;74:602-4.
2 Den Hollander N, Riley D, Befus D. Immunology of giardiasis. *Parasitology Today* 1988;4: 124-31.
3 Taylor GD, Wenman WM. Human immune response to Giardia lamblia infection. *J Infect Dis* 1987;155:137-40.