

Red blood cell transfusion in newborn infants

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Red blood cell transfusion is an important and frequent component of neonatal intensive care. The present position statement addresses the methods and indications for red blood cell transfusion of the newborn, based on a review of the current literature. The most frequent indications for blood transfusion in the newborn are the acute treatment of perinatal hemorrhagic shock and the recurrent correction of anemia of prematurity. Perinatal hemorrhagic shock requires immediate treatment with large quantities of red blood cells; the effects of massive transfusion on other blood components must be considered. Some guidelines are now available from clinical trials investigating transfusion in anemia of prematurity; however, considerable uncertainty remains. There is weak evidence that cognitive impairment may be more severe at follow-up in extremely low birth weight infants transfused at lower hemoglobin thresholds; therefore, these thresholds should be maintained by transfusion therapy. Although the risks of transfusion have declined considerably in recent years, they can be minimized further by carefully restricting neonatal blood sampling.

Key Words: Anemia; Blood grouping; Cross-matching; Erythrocyte; Hemorrhagic shock; Hyperkalemia

Neonatal intensive care, particularly for very low birth weight infants, is characterized by the frequent use of red blood cell (RBC) transfusions. The objective of the present statement, which replaces a previous Canadian Paediatric Society document published in 2002,⁽¹⁾ is to provide evidence-based recommendations for the use of RBC transfusions in newborn infants. The specific goals of safely reducing transfusion exposures while avoiding both acute and chronic consequences of RBC depletion have been influenced since 2002 by findings reported in comprehensive clinical trials⁽²⁻⁵⁾ and a Cochrane review.⁽⁶⁾ Indications for exchange transfusion are not addressed in the present statement.

The most frequent indications for blood transfusion in the newborn are for the acute treatment of perinatal or surgical hemorrhagic shock and as 'top-ups' for the recurrent correction of anemia of prematurity. The environment and culture of blood transfusion have changed significantly since the emergence of HIV-AIDS, with advances in transfusion medicine and subsequent reductions in donor exposure and risk leading to increasing confidence in the blood supply.⁽⁷⁻⁹⁾

The literature published on this topic between 1976 and 2012 was reviewed using MEDLINE, the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register. PubMed clinical series algorithms for therapy, diagnosis and prognosis were used, as appropriate, to explore each of the statements attributed with a level of evidence. For therapeutic recommendations, Cochrane reviews were given preference and updated as appropriate.

TRANSFUSION THERAPY

Blood products for transfusion in Canada are regulated by Health Canada and issued by Héma-Québec and the Canadian Blood

Les transfusions de culot globulaire aux nouveau-nés

La transfusion de culot globulaire est un élément important et fréquent des soins intensifs néonataux. Le présent document de principes traite des méthodes et des indications pour transfuser des culots globulaires au nouveau-né, d'après une analyse bibliographique. Les principales indications de transfusion sanguine au nouveau-né sont le traitement aigu du choc hémorragique périnatal et la correction récurrente de l'anémie de la prématurité. Le choc hémorragique périnatal exige l'administration immédiate de fortes quantités de culots globulaires, mais il faut tenir compte des effets d'une transfusion massive sur d'autres composants sanguins. Grâce à des essais cliniques sur les transfusions en cas d'anémie de la prématurité, il est désormais possible de compter sur des lignes directrices, même s'il reste beaucoup d'incertitude. D'après des données dont la qualité de preuves est faible, l'atteinte cognitive pourrait être plus grave au suivi chez les nouveau-nés d'extrême petit poids à la naissance qui sont transfusés à des seuils d'hémoglobine bas. Il faut donc maintenir ces seuils par thérapie transfusionnelle. Même si les risques de transfusion ont diminué considérablement ces dernières années, on peut les réduire encore davantage en limitant soigneusement les ponctions capillaires néonatales.

Services to accredited sites.^(10,11) Transfusion in Canada is now universally component-specific, such that after collection in anti-coagulant media, RBCs are separated from other blood components. The buffy coat production method, with saline, adenine, glucose and mannitol additive solution for RBCs, is currently used by the Canadian Blood Services. At Héma-Québec, some RBC concentrates are prepared in additive solution 3. Differences in collection, storage and distribution techniques may affect the hematocrit of packed RBCs and the availability of other blood components. Fresh whole blood is no longer offered by transfusion services; stored RBCs are safe and effective for up to 42 days⁽¹²⁾ and permit the use of multiple dedicated-donor packs.⁽¹³⁾ However, the process of multiple preallocation is wasteful and, given the falling risk of transfusion-transmitted infection, may ultimately be discontinued.

Preventing adverse effects of RBC transfusion

Despite recent advances in screening and pathogen inactivation, RBC transfusion is the transplantation of active tissue and cannot be entirely risk free. The risks of transfusion can be classified as follows:⁽⁷⁻⁹⁾

- Transfusion-transmitted infections (viral, bacterial, parasitical or prional),
- The adverse effects of leukocytes (including immunomodulation, graft-versus-host disease; transfusion-related acute lung injury and alloimmunization),
- Acute volume or electrolyte disturbances, and
- Blood group incompatibilities (often mistransfusion errors).

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These risks are generally reduced by the processes of donor selection, and further reduced by the screening, cross-matching and (if and when approved) pathogen inactivation practices conducted by the Canadian Blood Services and Héma-Québec. The combined risk of RBC contamination with viruses (eg, hepatitis A, B and C, HIV and human T cell lymphotropic viruses) is of the order of one in one to 1.3 million.(9)

For newborn transfusion, there are specific considerations for blood-banking procedures.(13,14) Newborns, particularly extremely low birth weight infants who are most exposed to transfusion, are already immunologically compromised and neurodevelopmentally vulnerable. All transfusion-transmitted infections put the newborn at risk, but cytomegalovirus (CMV) infection may have serious consequences for more immature infants. The risk of CMV infection is reduced by universal leukoreduction, practiced in Canada since 1998. Most centres now γ -irradiate blood to deactivate lymphocytes and prevent graft-versus-host disease, which is rare in newborn infants. Hemolytic transfusion reactions are also rare in the newborn;(15) maternal isohemagglutinins are occasionally present in the first two months of life(16) but infant alloantibodies are rarely formed before six months of age.(15) Transfusion-related acute lung injury is also rare but is the subject of ongoing review.(17)

Administering RBC transfusions in newborns

Blood for neonatal transfusion is often issued as group O packed RBCs with compatible infant Rh type. Alternatively, non-group O infants may receive non-group O RBCs if passive maternal anti-A or anti-B is not detected in an infant's serum or plasma.(13) All birthing centres must be supported by transfusion services prepared to issue uncross-matched group O Rh-negative blood in a perinatal emergency. The hematocrit of packed RBCs with buffy coat preparation is approximately 60%.

Pretransfusion testing is limited to ABO grouping and Rh typing, with a screen for antibodies of maternal origin (direct and indirect antiglobulin tests). Unnecessary cross-matching can often be avoided with careful reference to blood bank guidelines: if an infant's initial antibody screen is negative, it is generally not necessary to repeat the screen up to four months of age.(13)

RBC transfusions for infants are issued in bags or syringes, and are administered by infusion pump. Rewarming is unnecessary and a limit of 4 h is applied to each issue. Transfusion volumes of 10 mL/kg to 20 mL/kg have been conventional, although higher volumes may increase RBC volume by 50% and cause large fluctuations in hemoglobin levels and viscosity. Transfusion volumes of 20 mL/kg given at 7 mL/kg/h can be tolerated by newborns but the evaluation of this practice is limited;(18) a conservative maximum would be 5 mL/kg/h. An alternative approach is to calculate the volume of blood transfused by hemoglobin target selection, which has conventionally been 150 g/L in the early newborn period. Attempting to reach this target later in life (when the transfusion threshold has fallen to 75 g/L) results in unacceptably large transfusion volumes; a lower target (eg, 130 g/L) may, therefore, be selected. Smaller and more frequent blood transfusions have become more acceptable as the risks of donor exposure have declined. Given the current uncertainty regarding the neurodevelopmental effects of anemia (see Anemia, below), it may be preferable to keep hemoglobin levels relatively constant.

INDICATIONS FOR RBC TRANSFUSION IN NEWBORNS

Hemorrhagic shock

Most hemorrhagic shock in newborn infants occurs at birth. The condition is sometimes the result of a perinatal catastrophe or,

occasionally, a surgical or instrumental complication. Concealed blood losses from antepartum hemorrhage or fetomaternal bleeding are difficult to evaluate and may share both acute and chronic components.

Neonatal and perinatal blood loss from placental hemorrhage, twin-to-twin transfusion, fetomaternal hemorrhage, velamentous insertion of the cord or cord rupture differ from adult models of hemorrhagic shock in that bleeding is terminated by the delivery itself. Traumatic bleeding is rarely an ongoing contributor to hypotension. Recent advances in the management of adults have identified both the rapid and massive administration of fluids and the transfusion of stored RBCs as contributors to ongoing coagulopathy and further bleeding in uncontrolled traumatic hemorrhage.(19) In massive transfusion, in which the transfused blood virtually replaces blood volume, multiple component transfusions with equal volumes of plasma, platelets and RBCs are effective in reducing the coagulopathies attributable to the loss of these components. However, there is little evidence at present to support this treatment approach as best practice.

Perinatal hemorrhagic shock must be recognized and treated immediately. A general but unevaluated approach to emergency treatment includes partial restoration of the circulation with normal saline, at 10 mL/kg to 20 mL/kg, while awaiting the emergency provision of group O Rh-negative packed RBCs, which should be administered in similar volumes. A hemoglobin level only provides guidance when chronic bleeding has occurred. The collection of cord or pretransfusion blood for typing is helpful. Large volumes of fluid and blood should be administered cautiously and in a staged process: initially and rapidly, to restore circulation; then secondly and prudently, to maintain adequate circulation and blood hemoglobin content. The administration rate for emergency transfusion depends on the critical state of the circulation, and may range from an initial 1 min push of 20 mL to later stabilization rates of 10 mL/kg/h, depending on the state of recovery. A major risk of rapid and massive transfusion is hyperkalemia. Saline, adenine, glucose and mannitol-prepared blood has an additional supernatant potassium content of approximately 1 mmol/L/day of storage and, therefore, may approach 50 mmol/L at 42 days. This potassium load is rapidly distributed after transfusion and subsequent RBC uptake may even cause hypokalemia.(20) A threshold hemoglobin level for further transfusion has not yet been determined. A theoretical and unevaluated minimum is in the order of 60 g/L.(21) The use of cord blood for emergency transfusion has not been evaluated.(22)

Anemia

Anemic hypoxia occurs when the level of circulating hemoglobin is inadequate to meet the oxygen demands of tissue.(23) The circulation's ability to deliver oxygen to tissue is a function of blood flow, along with the amount and functional capabilities of hemoglobin. The level of hemoglobin at which anemic hypoxia occurs can depend on the functional ability of RBCs or of hemoglobin to accept, transport and unload oxygen at tissue oxygen tensions, functions which are, in turn, affected by RBC physiology, the nature of the hemoglobin itself and the environment in which it functions.(24) The RBCs and hemoglobin of stored blood are functionally impaired; some dysfunctions improve with time in the recipient's circulation.(25) Therefore, the point at which any infant is functionally anemic post-transfusion cannot be defined easily by blood hemoglobin content alone.

In healthy infants, mixed venous oxygen saturation is high (>75%) and there is plenty of reserve oxygen available in blood. Variations in blood oxygen content are easily accommodated by

changes in the microcirculation, regional blood flow and fractional increases in oxygen uptake.(26) When the requirements of the tissues are addressed by local regulation, the quantity of hemoglobin may be considered to be adequate. When mixed venous oxygen content is low, a point is reached when an increase in cardiac output and other compensatory redistributions of blood flow must occur to ensure oxygen delivery. This point, currently poorly understood or defined, could be considered to characterize the hemoglobin level below which an infant has a compensated anemia. Even less well defined is the point at which chronic anemia results in long-term injury.

Anemia of prematurity

Anemia of prematurity is, in part, an exacerbation of the physiological anemia of the newborn, combining a suppressed postnatal response to erythropoietin, increased blood sampling, short RBC span in the newborn and the rapid increase in blood volume with growth.(27) The rapid decline in hemoglobin concentration is most severe in infants of shortest gestational age. More than 90% of extremely low birth weight infants are transfused, and they receive an estimated average of five transfusions each.(6)

Hemoglobin threshold trials

Most neonatal blood transfusions are administered to maintain minimal, although ill-defined, levels of hemoglobin. Maintenance or 'top-up' transfusions are triggered by hemoglobin thresholds, which have been compared during clinical trials.(6) Restrictive (low) versus liberal (high) hemoglobin thresholds have only marginal impact on the frequency of transfusion or on the hemoglobin levels of recipients. This surprising result may be attributed to the large volumes transfused (generally 15 mL/kg), which can result in overlap among the hemoglobin levels of compared cohorts. Nevertheless, the largest trial (the Premature Infants in Need of Transfusion [PINT] study), which maintained different transfusion thresholds until death or discharge, succeeded in generating a difference of 11 g/L (95% CI 8 g/L to 13 g/L) between groups at four weeks of age and a hemoglobin nadir of 101 g/L versus 112 g/L. Table 1 summarizes the transfusion thresholds described in the Cochrane review,(6) which closely reflected findings in the PINT study.

Short-term outcomes of transfusion trials

Within the narrow confines of the hemoglobin thresholds used, the use of restrictive versus liberal transfusion practices does not appear to have a significant impact on the combined outcomes of mortality or major morbidities at first hospital discharge: bronchopulmonary dysplasia, signs of hemorrhagic or ischemic brain injury, or severe retinopathy of prematurity (RR 1.07 [95% CI 0.96 to 1.20]).(6) These trials did not evaluate hemoglobin thresholds <100 g/L in the first week of life or <75 g/L in older infants. There were no differences reported in the rate of weight gain- or growth-related outcomes. Some trial findings are at variance with observational studies. For example, the onset of necrotizing enterocolitis appears to be associated with a recent blood transfusion,(28) but the condition is, if anything, more common with restrictive transfusion policies (RR 1.62 [95% CI 0.83 to 3.13]).(6)

Follow-up outcomes of transfusion trials

Follow-up outcomes have been reported for two trials but are interpretable for only one.(4) No statistically significant differences in the primary outcomes of combined death or disability were reported at 18 to 21 months corrected gestational age (RR restrictive:liberal 1.17 [95% CI 0.94 to 1.47]). However, a post hoc interpretation with a less severe definition of the Bayley II mental

TABLE 1
Suggested hemoglobin levels and hematocrit thresholds for transfusing infants with anemia of prematurity

Postnatal age	Respiratory support*	No respiratory support
Week 1	115 (35)	100 (30)
Week 2	100 (30)	85 (25)
Week 3 and older	85 (25)	75 (23)

Data presented as hemoglobin, g/L (hematocrit, %). *Respiratory support is defined as an inspired oxygen requirement in excess of 25% or the need for mechanical increase in airway pressure (Adapted from reference 6)

developmental index (a cut-off at <85 versus <70) favoured the use of high hemoglobin thresholds with resultant effect on this primary outcome (RR 1.21 [95% CI 1.01 to 1.44]). Until new information becomes available, it would be prudent to maintain hemoglobin levels above the thresholds described in Table 1.

Clinical indicators, signs of anemia and transfusion therapy

Apart from hemoglobin or hematocrit, there are no satisfactory clinical or laboratory guides to assist the decision to transfuse. Hemoglobin level is directly related to functional measures such as oxygen availability,(29) fractional oxygen extraction(30) and RBC transport,(31) but these predictable effects have not been clearly demonstrated to be better indicators for transfusion. Physiological compensations in systemic oxygen transport (eg, regional blood flow or oxygen transport or changes in cardiac output[31,32]) have not been adequately evaluated as predictors of neonatal well-being. Apneic events in unselected monitored preterm infants have been reduced immediately by transfusion;(33) however, the effect may be attributable to volume expansion(29) and was not observed in a careful study restricted to anemic preterm infants transfused for apnea(34) or reflected in transfusion trials.(6) In the most anemic infants, transfusion leads to minor reductions in heart and respiratory rates.(35) Such marginal benefits may be justified on an individual basis as an indication for transfusing an infant who is intolerant of cardiorespiratory stress. Within the hemoglobin limits under study, there were no effects of transfusion on the rate of infant weight gain.(6)

Erythropoietin

Early administration of erythropoietin to stimulate erythropoiesis in preterm infants slightly reduces the need for RBC transfusions and the volumes transfused. However, because most trials enrol infants who may already have been transfused, such reductions are of limited clinical importance. There may be a significant increase in the risk of severe retinopathy of prematurity.(36) At present, there is little support for the use of erythropoietin, except for families who withhold consent to transfuse with blood products.

Hematinic support

Iron supplementation at 2 mg/kg/day of elemental iron, introduced between four and six weeks of age at the onset of reticulocytosis, results in higher hemoglobin levels and iron stores after six months of age.(37) Higher doses are not helpful, but earlier use may result in higher hemoglobin levels. No other hematinic supplements have been shown to be effective.

CONSENT

Transfusion of blood products requires discussion of preferences and, except in emergencies, the consent of a child's parent or guardian. Members of certain faiths, in particular Jehovah's Witnesses, will generally not consent to the administration of

blood or blood products to family members, and particular care is required when consulting with parents or their counsellors about care options. An individualized, personal approach to evaluating the potential risks and benefits of transfusion is needed. Recourse to alternative or preventive strategies, such as placental transfusion, limited blood draws, erythropoietin and optimizing hematinics, may become the focus of patient management. However, the limited effectiveness and potential risks and benefits of departing from conventional care must be carefully evaluated and presented to families. Some preparations of erythropoietin contain human albumin. See the Canadian Paediatric Society's statement 'Treatment decisions regarding infants, children and adolescents' for guidance in situations in which there is a conflict in decision making or in which a health care team believes that parental decisions may not be in a child's best interest. (38)

RECOMMENDATIONS

For policy-makers:

- Blood products for transfusion of the newborn must be provided by an agency regulated by Canadian public health authorities.

For clinicians:(39)

- Group O Rh-negative blood may be used in the emergency transfusion of newborns. Otherwise, either group O Rh-compatible or group-specific Rh-compatible blood must be used. Starting at four months postnatal age, cross-matching of donor blood is required. (Strong Recommendation)
- In cases of massive hemorrhage, for which a large volume of blood may be required, care should be taken to avoid

hyperkalemia and dilution of coagulation factors, using combined replacement with fresh frozen or frozen plasma, as necessary. (Strong Recommendation)

- 'Top-up' transfusions should be used to maintain hemoglobin levels >75 g/L in convalescent preterm infants. (Moderate Recommendation)
- For infants in the first and second week of life, minimum hemoglobin levels of 100 g/L and 85 g/L, respectively, are recommended. (Weak Recommendation)
- Infants needing respiratory support may require transfusion at higher hemoglobin thresholds (see Table 1). (Weak Recommendation)
- Infants with cyanotic heart disease or similar hemodynamic disorders may require transfusion at higher hemoglobin thresholds. (Weak Recommendation)
- Transfusions should not be used to improve weight gain or to address apnea of prematurity when hemoglobin levels are already in excess of recommended levels for maintenance. (Weak Recommendation)

Note: Information for parents, 'When your child needs a transfusion', can be accessed at www.caringforkids.cps.ca

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