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BACKGROUND

While the practice of transfusion of blood products to neonatal and pediatric recipients has much in common with the transfusion of blood products to adults, there are several important differences and special circumstances. This chapter highlights the most common considerations that are unique to this group of patients.

NORMAL LEVELS OF HEMOGLOBIN AND COAGULATION FACTORS

An infant's hemoglobin concentration is approximately 165 g/l at birth, and increases to a mean of 184 g/l within 24 hours. During the first three months of life, hemoglobin decreases to approximately 115 g/l (Table 1). Preterm infants show a greater decrease. By age 12, the hemoglobin levels of healthy children are the same as those of adults (Table 2).

Table 1: Normal hemoglobin values for infants

Age	Hemoglobin concentration (g/l) (mean (- 2 SD))		
	Preterm*		Term
	1.0-1.5 kg	1.5-2.0 kg	
2 weeks	163 (117)	148 (118)	165 (125)
1 month	109 (87)	115 (82)	140 (100)
2 months	88 (71)	94 (80)	115 (90)
3 months	98 (89)	102 (93)	115 (95)
* Preterm infant is defined as an infant less than 37 weeks gestational age. Normal values for preterm infants will depend on gestational age. Normal values may differ depending on the laboratory performing the investigations.			
This table was extracted with permission from Nathan and Oski's Hematology of Infancy and Childhood, 7th Edition (2008). ¹			

Table 2: Normal hemoglobin values for infants and children

Age	Sex	Hemoglobin concentration (g/l) (mean (- 2 SD))
0.5 to 2 years	Both	120 (105)
2 to 6 years	Both	125 (115)
6 to 12 years	Both	135 (115)
12 to 18 years	Female	140 (120)
	Male	145 (130)
> 18 years	Female	140 (120)
	Male	155 (135)

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Age	Sex	Hemoglobin concentration (g/l) (mean (- 2 SD))
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Over the period from birth to six months of age, the concentrations of the vitamin K-dependent factors (factors II, VII, IX, X) and the vitamin K-dependent inhibitors of coagulation (proteins C and S) are lower than adult levels (Table 3), but gradually increase. By age six months, the concentrations of coagulation factors, contact factors and natural coagulation inhibitors have reached approximately those of adults.

Table 3: Normal reference ranges for coagulation factor assays and screening tests

Coagulation test or factor assay	Age	Age
	1 to 3 days	4 days to 18 years
Factor II	0.41 - 0.73 IU/ml	0.83 - 1.47 IU/ml
Factor V	0.64 - 1.54 IU/ml	0.71 - 1.68 IU/ml
Factor VII	0.52 - 1.07 IU/ml	0.57 - 1.59 IU/ml
Factor VIII	0.83 - 3.29 IU/ml	0.56 - 1.72 IU/ml
Factor IX	0.35 - 0.97 IU/ml	0.74 - 1.66 IU/ml
Factor X	0.46 - 0.75 IU/ml	0.69 - 1.54 IU/ml
Factor XI	0.07 - 0.79 IU/ml	0.63 - 1.52 IU/ml
Factor XII	0.13 - 0.97 IU/ml	0.40 - 1.49 IU/ml
	<3 months	3 months to 18 years
Fibrinogen	1.6 - 4.0 g/L	1.9 - 4.3 g/L
aPTT	25 - 45 sec	24 - 36 sec
INR	0.90 - 1.60	0.80 - 1.20
TCT	<21 sec	<21 sec

Abbreviations: International normalized ratio (INR); activated partial thromboplastin time (aPTT); thrombin clotting time (TCT).

PRE-TRANSFUSION TESTING

For the purposes of transfusion medicine, a neonate is defined as an infant under four months of age. The pre-transfusion testing required for neonates is more limited than that required for older infants, children and adults. For neonates, the required testing includes ABO and Rh(D) typing and an antibody screen. The determination of the ABO group of a neonate is based on red blood cell typing only. Plasma or serum typing ("reverse" group) is not performed because ABO antibodies initially present in the blood after birth are of maternal, and not neonatal, origin. If a non-Type O neonate from a Type O mother is to receive group-specific red blood cell transfusion, the neonate's serum or plasma must be tested for maternal anti-A or anti-B, and the choice of blood must take into consideration both the neonate's ABO group and the maternal antibodies present in the neonate's circulation. Some transfusion medicine services perform this testing and transfuse group-specific units, whereas others use only Type O red blood cells for neonates due to this complexity in the choice

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of ABO blood group for neonatal red blood cell transfusions. The Rh(D) type of red blood cell units must be compatible with both mother and infant. There is no need to give O-negative red blood cells to all neonates as only a small proportion of the population is Rh(D) negative.

The antibody screen is performed to detect unexpected red blood cell antibodies and may be performed using either a neonatal or a maternal blood specimen. Initially, any antibodies present in neonatal blood are maternal in origin. Because of the infant's immature immune system, if the initial screen is negative, it is not necessary to repeat it during the initial hospitalization up to four months of age. Furthermore, if the antibody screen for a neonatal patient is negative, the crossmatch may be omitted to decrease iatrogenic blood loss.

RED BLOOD CELL TRANSFUSION

Neonatal Recipients

Indications

The indications for red blood cell transfusion in neonates differ from those for children and adults, for several reasons including the infant's small blood volume, physiologic anemia of infancy, decreased production of endogenous erythropoietin, and the infant's inability to tolerate minimal physiologic stress. The indications for transfusion in neonates have been well-studied; nevertheless, the indications remain somewhat controversial for several reasons. These reasons include:

- difficulty determining when a neonate may benefit from a transfusion because of the varying hemoglobin levels and hemoglobin type (HbF versus HbA);
- difficulty in assessing the neonate for clinical indications for transfusion;
- lack of consensus of how significant symptoms are defined, and;
- the suggestion that the hemoglobin or hematocrit concentration may not accurately reflect the red blood cell mass in preterm and/or ill newborns.

Various publications exist that provide guidelines for red blood cell utilization in neonates.²⁻⁴ In general, neonates should be transfused if they have:

- acute blood loss of >10% blood volume;
- hemoglobin less than 80 g/l in a stable newborn with symptoms of anemia (apnea, bradycardia, tachycardia, decreased vigor, poor weight gain); or
- hemoglobin less than 120 g/l in an infant with respiratory distress syndrome or congenital heart disease.

There are conflicting data on the usefulness of clinical signs in the assessment of the need for red blood cell transfusion in a premature infant. The Premature Infants in Need of Transfusion (PINT) study in 2006 and a follow-up study in 2009 showed that a restrictive transfusion policy in infants weighing less than one kilogram did not have any adverse effect on short term or follow up mortality or morbidity.^{5, 6} The effect on neurodevelopment and cognitive delay is not yet clear. Thresholds for preterm neonatal transfusion have been set by the Canadian Paediatric Society (Table 4). It is recommended that these transfusion thresholds be maintained until further evidence is available.

Table 4. Suggested transfusion thresholds for neonates with anemia of prematurity. Adapted from the Canadian Paediatric Society Position Statement.⁴

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Postnatal age	Hemoglobin, g/l (hematocrit, %)	
	With respiratory support*	No respiratory support
0 to 7 days	115 (35)	100 (30)
8 to 14 days	100 (30)	85 (25)
>14 days	85 (25)	75 (23)

*Respiratory support is defined as an inspired oxygen requirement in excess of 25% or the need for mechanical increase in airway pressure

The usual dose of red blood cells is 10 to 20 ml per kg of recipient body weight, depending on the product used and the volume the infant can tolerate. In general, a dose of 15 ml/kg can be expected to raise the baby's hemoglobin (Hb) concentration by about 20 g/l. Red blood cells stored in SAG-M additive solution have a hematocrit of approximately 0.7 l/l. If supernatant fluid is removed from the red blood cell unit, then the amount transfused should be decreased accordingly.

Selection of red blood cell units

In the past, it was common practice to transfuse neonates with relatively fresh red blood cells for two reasons: (1) because of the increased amount of plasma potassium in stored red blood cells; and (2) because of the decreased levels of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells after extended storage. These concerns are valid for infants receiving large-volume transfusions (>20 ml/kg) as the potassium content of stored blood when administered rapidly may be lethal for a neonatal patient. In contrast, infants receiving smaller volume transfusions (<20 ml/kg) over three or four hours, in most cases, do not require fresh red blood cells. In fact, widespread practice has demonstrated the safety of assigning a fresh red blood cell unit to a neonatal patient and using aliquots of this same unit up to its normal expiry date for subsequent small-volume red blood cell transfusions.⁷ This strategy is beneficial as it contributes to decreased donor exposure for the infant. A more recent study showed that the use of fresh red blood cells compared with standard blood bank practice did not improve outcomes from major neonatal morbidities including necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia or intraventricular hemorrhage in premature very low-birth-weight infants requiring a transfusion.⁸

If the potassium content of stored blood remains a concern in rapid and massive transfusion for particular patients, the risk can be diminished by supernatant reduction or washing the red blood cell aliquots, negating the requirement for fresh red blood cells. In addition, potassium filters are available and may be used if washing or supernatant reduction are not feasible.

Donor exposure should be limited to decrease both the infectious and non-infectious risks of transfusion. Various strategies may be used, of which the most important is to administer transfusions only when absolutely necessary. For neonates who do require red blood cell transfusions, it is generally agreed that the best way to decrease donor exposure is by the use of a dedicated donor unit with multiple satellite packs or with the use of a sterile docking device. Because of the small amount of blood required by a neonate for each transfusion, repeated transfusions may be given to the same patient from a single unit.

Additive solutions

Various additive solutions for the storage of red blood cells are available internationally, including AS-3, AS-1 and saline-adenine-glucose-mannitol (SAGM). Table 5 lists the components of these solutions. In Canada, SAGM is the additive solution used for the storage of red blood cells and citrate phosphate-dextrose (CPD) is the anticoagulant. When additive solutions were first introduced, concerns about the safety of transfusing red blood cells stored in these solutions into neonatal patients were raised. Since their introduction, however, many years

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of experience as well as several studies have confirmed that small volume transfusions (< 20 ml/kg) of unmodified red cells stored in additive solutions are safe.⁹ For neonates receiving massive transfusion or those with renal insufficiency it is often recommended that the additive solution be removed.

Table 5: Composition of additive solutions for red cell concentrates

Components (mg/100 ml)	SAG-M	AS-1	AS-3
NaCl	877	900	410
Dextrose	900	2200	1100
Adenine	16.9	27	30
Mannitol	525	750	-
Sodium citrate	-	-	588
Citric acid	-	-	42
Sodium phosphate (monobasic)	-	-	276
Approved storage time (days)	42	42	42
Primary anticoagulant-preservative	CPD	CPD	CP2D

Use of erythropoietin

There have been many controlled trials evaluating the use of recombinant human erythropoietin (rHuEPO) in premature infants for the treatment and prevention of anemia of prematurity. However, their results vary, perhaps due to different patient populations and dosing schedules, so the potential benefit remains controversial. A meta-analysis concluded that it is premature to make firm recommendations for the use of rHuEPO in patients with anemia of prematurity.¹⁰ Some studies have indicated that erythropoietin administration might decrease the number of transfusions that low birth weight infants receive. However, it is likely that donor exposure may be kept just as low through the use of a dedicated donor unit used until its expiration date of 42 days. This should be combined with careful attention to the amount of blood withdrawn for laboratory testing and adherence to evidence-based transfusion guidelines.^{4, 11}

Pediatric recipients

The principles used to guide the decision to transfuse red blood cells to infants older than four months of age and children are essentially the same as for adults (See Table 6 and Chapter 2 of this *Guide*). In general, young children have lower hemoglobin concentrations than adults, with a child of six months of age having an average hemoglobin level of 95–115 g/l and a child of two years of age having a hemoglobin level of 115–125 g/l (Table 2). The physiologic responses of children to anemia have not been well-studied but are thought to be similar to adults.

Table 6: Guidelines for transfusion of red blood cells in pediatric patients more than four months of age.

1. Acute blood loss >15% total blood volume
2. Hemoglobin <70 g/l with symptoms of anemia
3. Significant preoperative anemia when other corrective therapy is not available

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- | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4. Hemoglobin <130 g/l on extracorporeal membrane oxygenation |
| 5. Chronic transfusion programs for disorders of red blood cell production (such as β -thalassemia major and Diamond-Blackfan syndrome unresponsive to therapy) |

Adapted from *Paediatric Transfusion: A Physician's Handbook* (2009)¹² and Roseff et al. (2002).¹³

However, young infants may be less able to tolerate rapid blood loss, because of their limited ability to respond to hypovolemia by increasing myocardial contractility. This is complicated by the fact that the severity of acute blood loss may be underestimated in children (as well as in older children and young adults). On the other hand, children rarely have underlying cardiovascular or respiratory diseases and so often tolerate low levels of hemoglobin well, particularly if the anemia develops slowly.

In general, there is no single value of hemoglobin concentration that indicates that a transfusion is required and clinical evaluation is of critical importance. The major indication for red blood cell transfusions is the prevention or alleviation of symptoms or signs of inadequate tissue oxygen delivery. Red blood cells are generally dosed based on the child's weight (i.e. 10 ml/kg for packed red blood cells and 15 ml/kg for red blood cells in SAGM or other additive solutions).

Directed donation

A directed donation is when a donor donates for a specified recipient of his/her choice. Canadian Blood Services only allows directed donations from a parent/legal guardian to their minor child to alleviate psychological stress. There is currently no evidence that directed donations are either safer or less safe than donations from regular, anonymous allogeneic donors. Directed donations may be required in circumstances where only family members have a blood type that is a match for a very rare recipient, but are otherwise discouraged as they offer no safety benefit.

The use of directed donation is declining at Canadian Blood Services, with less than a hundred red blood cell units issued in 2015; the majority of those units were discarded. The use of directed donations should be discouraged. The particular risks associated with directed donations need to be disclosed to the donor and to the recipient when obtaining informed consent for transfusion. These risks include an increased risk of transfusion associated graft-versus-host disease (see Chapter 15 of this Guide) as well as all other risks that may be associated with any allogeneic transfusion.

PLATELET TRANSFUSIONS

Neonatal recipients

As for adults, platelet transfusions are indicated to prevent or decrease bleeding associated with quantitative or qualitative platelet disorders. The decision to transfuse platelets to an infant or child should be made with consideration to the etiology and natural history of the thrombocytopenia. Guidelines for platelet transfusions for children are essentially the same as those for adults.¹⁴ See chapters 2 and 18 of this *Guide* for more information.

It is reasonable to assume that neonates may require platelets at a higher platelet threshold because of their increased bleeding tendency and, in particular, their higher risk of intracranial hemorrhage. Furthermore, preterm infants or infants with other co-morbidities may have an increased risk of bleeding. Although adequate data are lacking, various guidelines based on expert opinion have been published to indicate when platelets should be transfused to neonates. An example is shown in Table 7. In general, a transfusion trigger of $20 \times 10^9/l$ may be used for stable term infants with a slightly higher trigger (i.e. 30 to $50 \times 10^9/l$) used for preterm infants. Infants who are bleeding or who have a consumptive coagulopathy may require a higher platelet transfusion

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threshold to be used.

Table 7: Guidelines for platelet transfusion support of neonates. Reprinted with permission from: *Paediatric Transfusion: A Physician's Handbook*, 3rd edition.¹²

1. Stable patient, platelet count < 20 x 10 ⁹ /l
2. Unstable patient, platelet count 30 x 10 ⁹ /L to 50 x 10 ⁹ /l
3. Infant with active bleeding, or invasive procedure, platelet count < 50 x 10 ⁹ /l

Platelets are generally given in doses of 5–10 ml per kg, which should be expected to increase the platelet count of a full-term infant by 50–100 x 10⁹/l. Ideally, type-compatible platelets should be given. If the plasma in the platelet product is not compatible with the neonate's red blood cells, the platelet product should be plasma-reduced to avoid the risk of hemolytic transfusion reaction.

Childhood idiopathic thrombocytopenic purpura (ITP)

Children with ITP should be transfused with platelets only if severe bleeding is present as the transfused platelets will have a shortened survival and minimal benefit.¹⁵

PLASMA TRANSFUSIONS

Although studies are limited, it is generally agreed that children should be transfused with plasma products based on the same principles as those used for adults (See Chapter 2 of this *Guide*). Infants under six months of age have decreased levels of vitamin K-dependent coagulation factors and inhibitors of coagulation (factors II, VII, IX, X, protein C, protein S, so it may be reasonable to transfuse plasma to infants younger than six months of age earlier than one would for older children and adults.

The primary indication for transfusion of plasma in a neonate or young child is the correction of bleeding due to multiple acquired coagulation factor deficiencies. Where feasible, the decision to transfuse plasma should be guided by the clinical situation and by appropriate laboratory testing (Table 8). The use of plasma is not recommended when the sole purpose of the transfusion is to treat hypovolemia. Additionally, plasma transfusion should be avoided when a safer product can be used to obtain the same therapeutic goal. For example, virus-inactivated recombinant factor concentrates are preferable for the treatment of any isolated coagulant factor deficiency. Plasma is normally given at a dose of 10 to 15 ml per kg. This dose can be expected to increase factor activity by 20% in an infant without ongoing consumption of coagulation factors.

Table 8: Guidelines for the transfusion of plasma. Reprinted with permission from *Paediatric Transfusion: A Physician's Handbook*, 3rd edition.¹²

1. Replacement therapy in a bleeding patient or one about to undergo invasive procedure
2. When specific factor concentrates are not available, including but not limited to Factors II, VII, X, and XI, protein C or S
3. PT/INR >1.5 x mid-range of age-related normal value and/or PTT >1.5 x top of age-related normal value in a bleeding patient or one about to undergo invasive procedure
4. During therapeutic plasma exchange when Plasma is indicated
5. Reversal of warfarin in an emergency situation, such as before an invasive procedure with active bleeding (consider use of prothombin complex concentrate if available)

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MASSIVE TRANSFUSION IN NEONATES

Massive blood transfusion is defined as the replacement of greater than one blood volume in 24 hours. The blood volume of a full-term infant is approximately 85 ml per kg and that of a preterm infant is approximately 100 ml per kg. In the neonate, massive transfusion generally occurs in the following situations:

- cardiopulmonary bypass (CPB);
- extra-corporeal membrane oxygenation (ECMO); and
- exchange transfusion.

Cardiopulmonary bypass

Infants and children may undergo CPB during surgical correction of congenital cardiac abnormalities. These children are generally exposed to large numbers of blood products in the perioperative period. The infant is heparinized during the surgery with heparin levels adjusted according to the activated clotting time (ACT). During the surgery, a volume of blood that is two to three times the patient's blood volume is passed through the circuit. The prime needed for CPB is generally red blood cells and plasma in infants and albumin in children. During the passage through the circuit, platelets and neutrophils may become activated and coagulation factors may be consumed. Following the surgery, blood product support (red blood cells, platelets, cryoprecipitate) should be provided as required.

Extra-corporeal membrane oxygenation

ECMO is a type of cardiopulmonary bypass with a membrane oxygenator that is used to temporarily support infants with respiratory or cardiac failure. Infants tend to require ECMO for an average of five days but in rare cases it may be used for as long as 28 days. When the infant is placed on ECMO, albumin and group-specific (or Type O) red blood cells are used as the priming volume. To prevent clotting in the circuit, infants are heparinized while on ECMO. In addition, qualitative and quantitative platelet dysfunction occurs. Therefore, the infant's risk of hemorrhagic complications is high and it is generally recommended that platelet transfusions be given to maintain the platelet count greater than 100×10^9 per litre.

USE OF GAMMA IRRADIATED BLOOD PRODUCTS

Gamma irradiation of cellular blood products is used to eliminate the risk of transfusion-associated graft vs. host disease (TA-GVHD). The recommended radiation dose is 25 cGy to the central point of the blood pack with a minimum dose of 15 cGy to other parts, and a maximum dose of 50 cGy. Irradiation effectively damages T-lymphocyte DNA, thereby preventing further mitosis and the potential for TA-GVHD. However, it also irreparably damages the red blood cell membrane, which leads to an increased the rate of potassium loss, precipitates cellular hemolysis, and decreases red blood cell recovery. As a result, Canadian Blood Services and many Canadian hospitals have voluntarily chosen to follow the Council of Europe Standards, 19th Edition (2017) recommendations which state that:

*Red cell components may be irradiated up to 28 days after collection. Irradiated cells must be transfused as soon as possible, but no later than 14 days after irradiation, and in any case, no later than 28 days after collection.*¹⁶

Due to configuration of the Canadian Blood Services Laboratory Information System, red blood cell units selected for irradiation at Canadian Blood Services are ≤ 14 days from collection. The expiry date of irradiated red blood cells is 14 days from irradiation or 28 days after collection, whichever is sooner.¹⁷

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Irradiation increases potassium accumulation in the supernatant during storage. While this is not of concern for most patients, it can be problematic for neonatal and young pediatric patients, particularly in the setting of large-volume transfusions. Thus, red blood cell units for neonatal and young pediatric patients should be irradiated close to the time of issue or have the supernatant fluid removed if the red blood cell unit is more than 24 hours following irradiation. Generally accepted indications for the gamma irradiation of blood products for neonates and children are listed in Chapter 15 of this *Guide*.

USE OF CYTOMEGALOVIRUS (CMV) SERONEGATIVE BLOOD PRODUCTS

With current leukoreduction techniques during manufacturing, the rate of CMV transmission by transfusion is very low (estimated to be 1 in 13,575,000).¹⁸ In 2016, a systematic review and meta-analysis evaluated blood product leukoreduction with or without donor serology testing in risk reduction of transfusion-transmitted CMV (TT-CMV). In the 11 studies evaluated, there was no sign of increased risk, demonstrated by clinical and/or laboratory evidence of CMV infection, when comparing leukoreduction to CMV untested units (five studies), leukoreduction to CMV seronegative units (three studies), or leukoreduction alone versus leukoreduction plus CMV seronegativity (two studies).¹⁹ Based on these and other data, current recommendations of the National Advisory Committee for blood and blood products in Canada indicate that the provision of CMV-seronegative and leukoreduced blood products is necessary only in the setting of intrauterine transfusion.²⁰

This recommendation reflects the many routes by which congenital CMV infection can occur. These include: a) primary infection of a seronegative pregnant woman, b) reinfection of a seropositive woman or c) reactivation of CMV in a seropositive woman, with TT-CMV potentially implicated in the first two routes of infection. Fetal transfusion is one of the few clinical settings in which extremely prolonged survival of donor leukocytes have been described, increasing the possibility of CMV reactivation after transfusion of cells with latent infection.²¹ ²² For these reasons, along with the difficulty in detecting and monitoring fetal infection, a lack of effective in utero therapy and a high clinical burden of disease for the affected neonates, the recommendation is to continue to provide CMV seronegative leukoreduced blood products for fetal transfusion. This is the only indication for CMV seronegative blood products, and the quantity of tested units available reflects the rarity of intrauterine transfusions in Canada.

The use of CMV-seronegative blood products for transfusion in low birth weight neonates is not deemed necessary. The primary rationale is that CMV is common in this high-risk patient population given that CMV is excreted in breast milk. A prospective study involving 462 mothers of 539 infants with a birth weight less than or equal to 1,500 g demonstrated a maternal seroprevalence rate of 76.2%. Twenty seven of the 539 infants developed postnatal CMV infection secondary to CMV positive breast milk at 12 weeks, with five exhibiting symptomatic disease and three progressing to death.²³ Caretakers of premature infants understand the risk of CMV disease, and screening and monitoring for CMV disease is available. Effective antiviral agents are also available and allow pre-emptive and symptomatic treatment of patients with CMV infection or exposure. Among Canadian hospitals who have not used CMV-seronegative components for transfusion of low birth weight infants for many years, there has been no evidence of increased neonatal CMV disease. There is also no evidence of CMV transmission to fetuses or neonates due to transfusion of cellular blood products during pregnancy when the CMV status of the mother is unknown or negative.

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to **two credits**.

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We're here to answer your questions about the Clinical Guide to Transfusion. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the [Clinical Guide feedback form](#).

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