Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Patient blood management guidelines: module 6 - neonatal and paediatrics.

Bibliographic Source(s)

National Blood Authority (NBA). Patient blood management guidelines: module 6 - neonatal and paediatrics. Canberra ACT (Australia): National Blood Authority (NBA); 2016. 298 p. [401 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the levels of evidence (I, II, III-1, III-2, III-3, IV) and grades of recommendations (A-D, Practice Point) are provided at the end of the "Major Recommendations" field. The Clinical/Consumer Reference Group (CRG) also developed Expert Opinion Points related to the material covered in the background questions.

Effect of Red Blood Cell (RBC) Transfusion on Outcomes

Preterm and Low Birth Weight Infants (RBC Transfusion)

In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested (Grade C).[a, b, c]

In neonatal and paediatric patients, the decision to give a RBC transfusion should not be dictated by a Hb concentration alone.[d] The decision should also be based on assessment of the patient's underlying condition, anaemia-related signs and symptoms, and response to previous transfusions. Underlying conditions that may influence the decision to transfuse include acquired or congenital cardiac disease and severe respiratory disease. (Practice Point)

Neonatal units should use a procedural guideline[e] for RBC transfusion in preterm infants that includes the following:

- Age of infant
- Age-specific Hb reference ranges
- Hb or haematocrit
- Level of respiratory support

- Ongoing or anticipated red cell loss
- Nutritional status

(Practice Point)

In preterm infants requiring transfusion, there is insufficient evidence to support or refute the use of either a restrictive or liberal RBC transfusion strategy. (Practice Point)

In neonatal patients, calculate transfusion volume (mL) based on weight and desired Hb increment.[e,f] (Practice Point)

[a]See PP6 in the original guideline document for guidance on a restrictive strategy.

[b]Higher Hb thresholds may be appropriate in very low birth weight and preterm neonates.

[c]See PP2, PP3, and Appendix F in the original guideline document for guidance for preterm and neonates.

[d]See the National Guideline Clearinghouse (NGC) summary of the National Blood Authority (NBA) guideline Patient blood management guidelines: module 3 - medical.

[e]See Appendix F in the original guideline document.

[f]See Appendix G in the original guideline document.

Infants, Children and Adolescents (RBC Transfusion)

In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a,b,c] (Grade C)

For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:

- Age-specific Hb reference ranges
- Volume of transfusion and rate of administration
- Patient monitoring during and after transfusion
- Transfusion technique (e.g., use of syringe pumps)
- Recognition and reporting of adverse events

(Practice Point)

In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[d] suggests that, with a:

- Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available
- Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions
- Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate

(Practice Points)

In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.[e] (Practice Point)

In most paediatric patients over 20 kg, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.[f] (Practice Point)

In paediatric patients over 20 kg who are chronically transfused (e.g., haemoglobinopathies or bone marrow failure syndromes) a single-unit approach may not be appropriate. Instead, calculation of the transfusion volume (mL) should be based on weight and desired Hb increment. (Practice Point)

In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.[g] A template protocol is provided within the module.[h] (Practice Point)

[a]See PP6 in the original guideline document for guidance on a restrictive strategy.

[b]Higher Hb thresholds may be appropriate in very low birthweight and preterm neonates.

[c]See PP2, PP3, and Appendix F in the original guideline document for guidance for preterm and neonates.

[d]See the NGC summary of the NBA guideline Patient blood management guidelines: module 4 - critical care.

[e]See Appendix F and Appendix G in the original guideline document.

[f]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

[g]The use of the word 'protocol' is not strictly prescriptive.

[h]The template given in Appendix K of the original guideline document is intended for local adaptation.

Sickle Cell Disease (RBC Transfusion)

In children and adolescents with sickle cell disease who have been assessed to be at increased risk of stroke,[a] a program of prophylactic RBC transfusions should be used in order to reduce stroke occurrence.[b] (Grade A)

In paediatric patients with beta thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90–100 g/L.[c] (Practice Point)

Children and adolescents with sickle cell disease should be assessed for stroke risk using both transcranial Doppler ultrasonography and magnetic resonance imaging (MRI). (Practice Point)

[a]Assessed by transcranial Doppler ultrasonography and MRI.

[b]See PP11 in the original guideline document for methods of assessment.

[c]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

Anaemia Associated with Cancer (RBC Transfusion)

For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:

- Age-specific Hb reference ranges
- Volume of transfusion and rate of administration
- Patient monitoring during and after transfusion
- Transfusion technique (e.g., use of syringe pumps)
- Recognition and reporting of adverse events

(Practice Point)

In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[a] suggests that, with a:

- Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available.
- Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions.
- Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate.

(Practice Point)

In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.[b] (Practice Point)

In most paediatric patients over 20 kg, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.[c] (Practice Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 4 - critical care.

[b]See Appendix F and Appendix G in the original guideline document.

[c]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

Surgical (RBC Transfusion)

In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a,b,c] (Grade C)

In neonatal and paediatric patients, the decision to give a RBC transfusion should not be dictated by a Hb concentration alone.[d] The decision should also be based on assessment of the patient's underlying condition, anaemia-related signs and symptoms, and response to previous transfusions. Underlying conditions that may influence the decision to transfuse include acquired or congenital cardiac disease, and severe respiratory disease. (Practice Point)

In preterm infants requiring transfusion, there is insufficient evidence to support or refute the use of either a restrictive or liberal RBC transfusion strategy. (Practice Point)

For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:

- Age-specific Hb reference ranges
- Volume of transfusion and rate of administration
- Patient monitoring during and after transfusion
- Transfusion technique (e.g., use of syringe pumps)
- Recognition and reporting of adverse events

(Practice Point)

In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[e] suggests that, with a:

- Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available.
- Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions.
- Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate.

(Practice Point)

In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.[f] (Practice Point)

In most paediatric patients over 20 kg, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.[g] (Practice Point)

In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.[h] A template protocol is provided within the module.[i]

[a]See PP6 in the original guideline document for guidance on a restrictive strategy.

[b]Higher Hb thresholds may be appropriate in very low birth weight and preterm neonates.

[c]See PP2, PP3, and Appendix F in the original guideline documenet for guidance for preterm and neonates.

[d]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

[e]See the NGC summary of the NBA guideline Patient blood management guidelines: module 4 - critical care.

[f]See Appendix F and Appendix G in the original guideline document.

[g]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

[h]The use of the word "protocol" is not strictly prescriptive.

[i]The template given in Appendix K of the original guideline document is intended for local adaptation.

Critically Ill (RBC Transfusion)

In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a,b,c] (Grade C)

In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.[d] A template protocol is

provided within the module.[e] (Practice Point)

[a]See PP6 in the original guideline document for guidance on a restrictive strategy.

[b]Higher Hb thresholds may be appropriate in very low birth weight and preterm neonates.

[c]See PP2, PP3, and Appendix F in the original guideline document for guidance for preterm and neonates.

[d]The use of the word "protocol" is not strictly prescriptive.

[e]The template given in Appendix K in the original guideline document is intended for local adaptation.

Effect of Non-transfusion Interventions to Increase Hb Concentration on Outcomes

Preterm and Low Birth Weight Infants (Erythropoiesis Stimulating Agents [ESAs] with or without Iron)

In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised. (Grade C)

Preterm and Low Birth Weight Infants (Oral and/or Parenteral Iron)

Preterm and low birth weight infants should receive iron supplementation as necessary to achieve the recommended nutrient intake. However, routine supplementation in excess of the recommended nutrient intake, to reduce transfusion incidence, is not supported. (Practice Point)

Infants, Children and Adolescents (Oral and/or Parenteral Iron)

Infants and children should receive sufficient dietary iron to achieve the adequate intake or recommended daily intake. If the adequate intake or recommended daily intake cannot be met by dietary means, iron supplementation is advised. (Practice Point)

Infants and children in populations at high risk[a] of iron deficiency should be screened for this condition.[b] (Practice Point)

Infants and children with iron deficiency should be treated with iron supplements and dietary modifications. (Practice Point)

[a]See references 13 and 14 in the original guideline document.

[b]See section 3.6 in the original guideline document.

Cancer (ESAs with or without Iron)

In paediatric patients receiving chemotherapy, the *routine* use of ESAs is not advised. The use of ESAs may reduce transfusion incidence; however, the studies are underpowered to determine their effect on mortality and thromboembolic events, which are increased in the adult population.[a] (Practice Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

Kidney Disease (ESAs with or without Iron)

In paediatric patients with chronic kidney disease, ESA therapy to achieve a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient.[a,b,c] (Practice Point)

In adult patients with chronic kidney disease, ESA therapy to achieve a Hb target of >130 g/L is not recommended because of increased morbidity; therefore, it is sensible to apply this limit to paediatric patients.[a] (Practice Point)

ESA use is less effective in patients with chronic kidney disease who have absolute or functional iron deficiency.[a] (Practice Point)

Where ESAs are indicated for the treatment or prevention of anaemia in neonatal and paediatric patients, they should be combined with iron therapy. (Practice Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

[b]The KDIGO guidelines recommend a Hb target of 110–120 g/L for paediatric patients and state that individualisation of ESA therapy is reasonable because some patients may have improvements in quality of life at higher Hb concentration (see the NGC summary of the KDIGO clinical practice guideline for anemia in chronic kidney disease).

[c]The National Institute for Health and Care Excellence (NICE) guidelines recommend a Hb target of 100–120 g/L for children aged 2 years and older, and 95–115 g/L for children younger than 2 years of age (reflecting the lower normal range in that age group) (see the NGC summary of the NICE guideline Anaemia management in people with chronic kidney disease).

Sickle Cell Disease (Hydroxyurea)

In paediatric patients with sickle cell disease, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.[a,b] (Grade B)

In paediatric patients over 9 months of age with sickle cell disease, hydroxyurea should be offered to reduce vaso-occlusive pain crises and acute chest syndromes. (Practice Point)

[a]Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke.

[b]See R1 and PP21 of the original guideline document.

Surgical (ESAs with or without Iron)

In neonatal and paediatric surgical patients, an ESA should only be prescribed in consultation with a paediatric haematologist, and should be combined with iron therapy. (Practice Point)

Surgical (Oral and/or Parenteral Iron)

In surgical paediatric patients with or at risk of iron deficiency anaemia, preoperative iron therapy is recommended.[a] (Grade C)

In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiency[b] should be identified, evaluated and managed to minimise RBC transfusion.[c] (Practice Point)

To implement the previous Practice Point, patients should be evaluated as early as possible so that scheduling of surgery can be coordinated with optimisation of the patient's Hb and iron stores. (Practice Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

[b]Iron deficiency can be present with a normal Hb.

[c]See Appendix H in the original guideline document for further information on the optimal dosing strategy.

Critically Ill (ESAs with or without Iron)

In critically ill paediatric patients with anaemia, ESAs should not be *routinely* used.[a] (Practice Point)

[a]This point is based on the lack of effect of ESAs on mortality in critically ill adult patients. See the NGC summary of the NBA guideline Patient blood management guidelines: module 4 - critical care.

Critically Ill (Oral and/or Parenteral Iron)

Critically ill paediatric patients should receive iron supplementation as necessary to achieve the recommended nutrient intake. (Practice Point)

Effect of Blood Components on Outcomes

Preterm and Low Birth Weight Infants (Fresh Frozen Plasma [FFP])

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Preterm and Low Birth Weight Infants (Platelet Transfusion)

In neonatal and paediatric patients, the decision to transfuse platelets should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Cancer (Platelet Transfusion)

In neonatal and paediatric patients, the decision to transfuse platelets should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision

include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9$/L in the absence of risk factors, and at $<20 \times 10^9$/L in the presence of risk factors (e.g., fever, minor bleeding).[a] (Practice Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

Surgical (FFP)

In neonatal and paediatric patients undergoing cardiac surgery, the *routine* use of an FFP-based pump prime solution is not recommended, because it offers no advantages over an albumin-based solution in relation to postoperative blood loss, or perioperative transfusion requirements. (Grade C)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

For guidance on the use of FFP in specific patient groups, refer to:[a]

- The NGC summary of the NBA guideline Patient blood management guidelines: module 1 - critical bleeding/massive transfusion
- The NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative
- *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*
- Australian Haemophilia Centre Directors' Organisation (AHCDO) guidelines for patients with specific factor deficiencies (www.ahcdo.org.au)
- *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*

(Practice Point)

In neonatal and paediatric patients undergoing surgery, FFP is only indicated for treatment of active bleeding where coagulopathy is a contributing factor. Its use should be guided by clinical assessment, supplemented by point-of-care or laboratory testing. (Expert Opinion Point)

In general, neonatal and paediatric patients with an international normalised ratio (INR) ≤ 2 can undergo invasive procedures without any serious bleeding; however, higher INRs may be tolerated.[b] (Expert Opinion Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

[b]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

Surgical (Cryoprecipitate)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Cryoprecipitate should be used to treat active bleeding when the fibrinogen level is <1.5 g/L. A target level of 2 g/L may be appropriate in certain situations (e.g., when critical bleeding is occurring or anticipated).[a] (Expert Opinion Point)

[a]The template given in Appendix K of the original guideline document is intended for local adaptation.

Surgical (Platelet Transfusion)

In neonatal and paediatric patients, the decision to transfuse platelets should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

In general, neonatal and paediatric patients with a platelet count ≥50 × 10^9/L can undergo invasive procedures without any serious bleeding; however, lower platelet counts may be tolerated.[a] (Expert Opinion Point)

Specialist guidelines or haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with severe thrombocytopenia or coagulopathy. (Expert Opinion Point)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

Surgical (Fibrinogen Concentrate)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Surgical (Fibrinogen Concentrate Using a Different Fibrinogen Strategy)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Surgical (Combination Therapy)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Critically Ill (FFP)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

For guidance on the use of FFP in specific patient groups, refer to:[a]

- The NGC summary of the NBA guideline Patient blood management guidelines: module 1 - critical bleeding/massive transfusion
- The NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative
- *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*
- AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au)
- *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 3 - medical.

(Practice Point)

Critically Ill (Cryoprecipitate)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Critically Ill (Platelet Transfusion)

In neonatal and paediatric patients, the decision to transfuse platelets should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision

include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Critically Ill (Fibrinogen Concentrate)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Critically Ill (Combination Therapy)

In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting coagulation status, and congenital and acquired bleeding disorders. (Practice Point)

Use of Blood Conservation Strategies

Preterm and Term Infants (Placental Transfusion)

In preterm infants, deferring cord clamping for between 30 seconds and 3 minutes may reduce transfusion volume and incidence, and incidence of intraventricular haemorrhage. However, the effect of this practice on other outcomes (death, major morbidity and neurodevelopmental outcomes) is uncertain or unknown, particularly in extremely preterm infants (e.g., <28 weeks) and in those who require active resuscitation. (Practice Point)

In term infants, deferring cord clamping for at least 1 minute is likely to reduce the risk of iron deficiency at 3 to 6 months. This intervention should be considered in infants who do not require active resuscitation, provided that access to phototherapy for jaundice is available.[a] (Practice Point)

[a]See reference 19 in the original guideline document.

Haemolytic Disease (Intravenous Immunoglobulin [IVIg])

In neonates with haemolytic disease of the fetus and newborn, the use of IVIg is not recommended. (Grade B)

Neonates at risk of haemolytic disease of the fetus and newborn should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. (Practice Point)

In maternity patients with a fetus affected by haemolytic disease of the fetus and newborn who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. (Expert Opinion Point)

Surgical (Prevention of Hypothermia)

In paediatric patients undergoing surgery, measures to prevent hypothermia should be used.[a] (Grade B)

[a]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

Surgical (Acute Normovolaemic Haemodilution)

In paediatric patients, acute normovolaemic haemodilution has not been shown to reduce transfusion or improve clinical outcomes. However, if acute normovolaemic haemodilution is used, it requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion. (Practice Point)

Surgical (Intraoperative Cell Salvage)

In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, intraoperative cell salvage may be considered. If intraoperative cell salvage is used, it requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it. (Practice Point)

Surgical (Viscoelastic Point-of-Care Testing)

In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, viscoelastic point-of-care testing may be considered. (Practice Point)

Surgical (Antifibrinolytics)

In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, the use of antifibrinolytics is suggested.[a,b,c] (Grade C)

In paediatric patients undergoing surgery for scoliosis in whom substantial blood loss is anticipated, the use of antifibrinolytics may be considered.[b,c] (Grade C)

In paediatric patients undergoing craniofacial surgery in whom substantial blood loss is anticipated, the use of antifibrinolytics may be considered.[b,c] (Grade C)

In acutely bleeding critically ill paediatric trauma patients, tranexamic acid should be administered within 3 hours of injury.[c,d] (Practice Point)

In paediatric trauma patients aged under 12 years, a tranexamic acid dose of 15 mg/kg (maximum 1000 mg) infused intravenously over 10 minutes, followed by 2 mg/kg/hour (maximum 125 mg/hour) until bleeding is controlled or for up to 8 hours is suggested.[c,e] (Practice Point)

[a]Although there is evidence of a reduction in transfusion, there is insufficient evidence to determine the risk of thromboembolic complications.

[b]Tranexamic acid in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. Epsilon-aminocaproic acid is not licensed for use in Australia.

[c]See Appendix F and Appendix G in the original guideline document.

[d]See the NGC summary of the NBA guideline Patient blood management guidelines: module 4 - critical care.

[e]See the template given in Appendix K of the original guideline document, which is intended for local adaptation.

Surgical (Recombinant Activated Factor VII [rFVIIa])

In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, the *routine* use of rFVIIa is not recommended. (Grade C)

The administration of rFVIIa may be considered in the perioperative patient with life-threatening haemorrhage after conventional measures, including surgical haemostasis, use of antifibrinolytics and appropriate blood component therapy have failed.[a,b] (Practice Point)

[a]rFVIIa is not licensed for this use; its use should only be considered in exceptional circumstances.

[b]See the NGC summary of the NBA guideline Patient blood management guidelines: module 2 - perioperative.

Definitions

National Health and Medical Research Council (NHMRC) Evidence Hierarchy: Designations of Levels of Evidence According to Type of Research Question*

Level	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort study
III-1	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)	All or none[e]	All or none[e]
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial[f] • Cohort study • Case–control study • Interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm studies[g]	A retrospective cohort study	A case–control study

Level	Intervention[a]	Prognosis	Aetiology[b]
	• Interrupted time series without a parallel control group		
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

*Source: National Health and Medical Research Council (NHMRC) (2009). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. NHMRC. https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

[a]Definitions of these study designs are provided on pages 7-8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC, 2000).

[b]If it is possible and ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be utilised. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g., groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the 'aetiology' hierarchy of evidence should be utilised.

[c]A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[d]At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[e]All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[f]This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e., utilise A vs. B and B vs. C to determine A vs. C).

[g]Comparing single arm studies, i.e., case series from two studies. This would also include unadjusted indirect comparisons (i.e., utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Body of Evidence Matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence Base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Population/s studied in the body of evidence are similar to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population, and it is hard to judge whether it is sensible to generalise to the target population for the guidelines
Applicability	Directly applicable to the Australian healthcare context	Applicable to Australian healthcare context, with a few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to the Australian healthcare context

Grade of Recommendation

Grade A: Body of evidence can be trusted to guide practice.

Grade B: Body of evidence can be trusted to guide practice in most situations.

Grade C: Body of evidence provides some support for recommendation(s) but care should be taken in its application.

Grade D: Body of evidence is weak and recommendations must be applied with caution.

Practice Point/Expert Opinion Point: The systematic review found insufficient high-quality data to produce evidence-based recommendations, but the CRG felt that clinicians require guidance to ensure good clinical practice. The CRG also developed Expert Opinion Points related to the material covered in the background questions. Both the practice points and the expert opinion points are based on consensus among the members of the CRG.

Clinical Algorithm(s)

An algorithm titled "Critical bleeding protocol in infants and children" is provided in Appendix K of the original guideline document.

Scope

Disease/Condition(s)

Conditions requiring blood transfusion in neonatal and paediatric patients, including

- Anaemia
- Coagulation abnormalities (coagulopathy, thrombocytopenia, or platelet dysfunction)
- Haemolytic disease of the fetus and newborn (HDFN)
- Sickle cell disease
- Kidney disease
- Necrotising enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Bronchopulmonary dysplasia (BPD)

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Anesthesiology

Cardiology

Critical Care

Emergency Medicine

Family Practice

Hematology

Obstetrics and Gynecology

Oncology

Pediatrics

Surgery

Thoracic Surgery

Intended Users

Advanced Practice Nurses

Emergency Medical Technicians/Paramedics

Hospitals

Physician Assistants

Physicians

Guideline Objective(s)

To assist and guide health-care professionals in making clinical decisions about blood management in neonatal and paediatric patients

Target Population

Neonatal and paediatric patients with diseases or conditions requiring blood component transfusion

Note: All the recommendations, practice points and expert opinion points identified in this guideline also apply to Indigenous neonates and children. Additional information is given in Section 3.6 of the original guideline document to highlight the effect of social determinants in relation to anaemia in Indigenous children.

For purposes of this guideline, neonatal patients (≤28 days of age) are classified as follows:

- Preterm (<37 weeks of gestation)
- Extremely low birth weight (<1000 g)
- Very low birth weight (<1500 g)
- Low birth weight (<2500 g)

Paediatric patients (1 month to 18 years of age) are classified as:

- Infant (1–23 months of age)
- Child (2–12 years of age)
- Adolescent (13–18 years of age)

Interventions and Practices Considered

1. Red blood cell transfusion
2. Erythropoiesis-stimulating agents (ESAs) with or without iron
3. Oral and/or parenteral iron
4. Hydroxyurea
5. Fresh frozen plasma (FFP)
6. Platelet transfusion
7. Cryoprecipitate
8. Fibrinogen concentrate
9. Combination therapy (FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate)
10. Placental transfusion
11. Intravenous immunoglobulin (IVIg) therapy

12. Interventions to prevent hypothermia
13. Acute normovolaemic haemodilution
14. Intraoperative cell salvage during cardiac surgery
15. Viscoelastic point-of-care testing
16. Antifibrinolytic therapy
17. Recombinant activated factor VII

Major Outcomes Considered

- Mortality rate
- Transfusion volume (in transfused patients only) or transfusion incidence
- Thromboembolic events (stroke, deep vein thrombosis, pulmonary embolism [PE])
- Functional/performance status
- Bleeding events (major and minor)
- Transfusion-related serious adverse events
- Composite of mortality and severe morbidity
- New or progressive multiple organ dysfunctions (MODs)/failure
- Laboratory measures: haemoglobin (Hb), haematocrit (Hct), ferritin
- Chronic pain
- Vaso-occlusive events
- Tumour progression or recurrence
- Exchange transfusion incidence
- Intracranial/intraventricular haemorrhage
- Retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and necrotising enterocolitis (NEC)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Clinical Research Questions

Question Development Summary

Between February and November 2013, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the Expert Working Group (EWG), the independent systematic review expert and the Clinical/Consumer Reference Group (CRG). The process is described in greater detail in the technical reports accompanying these guidelines (see the "Availability of Companion Documents" field). The clinical research questions for systematic review were all intervention questions structured according to PICO (population, intervention, comparator and outcome) criteria. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG. The primary databases searched were EMBASE, Medline and the Cochrane Library Database. Additional searches were conducted on Health Technology Assessment and guideline Web sites (e.g., the National Institute for Health and Care Excellence [NICE] and the Canadian Agency for Drugs and Technologies in Health [CADTH]), clinical trial registries and PreMedline.

Background Material

Material relevant to background questions was gathered by consultants, registrars or nurses under the supervision of CRG members. Sources included medical textbooks, grey literature, published scientific and review articles, series yearbooks and other relevant medical literature; however, systematic review processes were not applied. The questions researched are listed in Box 2.2 in the original guideline document.

Review and Research

Systematic Review Process

Systematic reviews were undertaken to attempt to answer the single question specific to PBM in the neonatal and paediatric setting, and the three generic questions considered relevant to this module. The systematic review questions are listed in Box 2.1 in the original guideline document.

To answer these questions, comprehensive search strategies were designed, as detailed in Technical Report Volume 2 (see the "Availability of Companion Documents" field). Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant and literature recommended by expert members of the CRG. The search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically. However, implications for rural and remote areas, and the Indigenous population, have been considered and documented in the clinical guidance.

Literature Search Dates

The systematic reviews for this module included only data from studies that met the relevant inclusion criteria, were of adequate quality and were published before the literature search date for each question. Studies were excluded if they were published before 1995 (except primary studies if they were included as part of a systematic review). The rationale from the CRG was that papers published before 1995 were unlikely to reflect the current context of care, due to advances in neonatal and paediatric care. Identification of relevant evidence and assessment of evidence was conducted in accordance with the *Procedures and requirements for meeting the 2011 standard for clinical practice guidelines*.

Inclusion and Exclusion Criteria

The questions included in this module were crafted in such a way that they attempted to provide answers in clinically relevant areas of uncertainty. They were further refined through consultation among the systematic reviewer, CRG, NBA and the independent systematic review expert. Details of research question criteria are presented in Technical Report Volume 1 (see the "Availability of Companion Documents" field).

Briefly, inclusion criteria were determined from the PICO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded.

Number of Source Documents

See Appendix C in Technical Report Volume 2 for tables depicting literature search results and included studies for all review questions (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

National Health and Medical Research Council (NHMRC) Evidence Hierarchy: Designations of Levels of Evidence According to Type of Research Question*

Level	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort

Level	Intervention[a]	Prognosis	Aetiology[b]
III-1	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)	All or none[e]	All or none[e]
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial[f] • Cohort study • Case–control study • Interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm studies[g] • Interrupted time series without a parallel control group	A retrospective cohort study	A case–control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

*Source: National Health and Medical Research Council (NHMRC) (2009). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. NHMRC. https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

[a]Definitions of these study designs are provided on pages 7-8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC, 2000).

[b]If it is possible and ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be utilised. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g., groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the 'aetiology' hierarchy of evidence should be utilised.

[c]A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[d]At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[e]All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[f]This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e., utilise A vs. B and B vs. C to determine A vs. C).

[g]Comparing single arm studies, i.e., case series from two studies. This would also include unadjusted indirect comparisons (i.e., utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Body of Evidence Matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence Base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted

Component	A Excellent	B Good	C Satisfactory	D Poor
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Population/s studied in the body of evidence are similar to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population, and it is hard to judge whether it is sensible to generalise to the target population for the guidelines
Applicability	Directly applicable to the Australian healthcare context	Applicable to Australian healthcare context, with a few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to the Australian healthcare context

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Systematic reviews were undertaken to attempt to answer the single question specific to patient blood management (PBM) in the neonatal and paediatric setting, and the three generic questions considered relevant to this module. The systematic review questions are listed in Box 2.1 in the original guideline document. Refer to the Technical Reports (see the "Availability of Companion Documents" field) for details concerning the systematic review process and all evidence summary tables.

Classification and Assessment of Evidence

Studies identified for inclusion from the literature search were classified according to the National Health and Medical Research Council (NHMRC) levels of evidence hierarchy (see the "Rating Scheme for the Strength of the Evidence" field). To ensure that modules were based on the best available evidence, studies of higher levels of evidence (Levels I or II) were included in preference to those presenting lower levels of evidence (Levels III or IV). This was to minimise the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Studies identified from the systematic literature review were assessed according to NHMRC dimensions of evidence (see Table 2.4.2 in Technical Report Volume 1 [see the "Availability of Companion Documents" field]). There are three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain was derived directly from the literature identified for a particular intervention, aetiology or prognostic study. The other two domains were determined in consultation with the Clinical/Consumer Reference Group (CRG) as part of the study assessment process during the review of the evidence considered for module development. An aspect of the strength of the evidence domain is the level of evidence of the study, which was determined as described above using the NHMRC levels of evidence hierarchy (see the "Rating Scheme for the Strength of the Evidence" field).

Quality Appraisal

The methodological quality of the included studies was assessed using the criteria presented in Appendix 4.2 of Technical Report Volume 1. Quality assessment criteria varied according to whether included studies were systematic reviews, randomised controlled trials (RCTs), cohort studies or case–control studies. No weighting of quality criteria was applied, but studies that met all criteria, or all but one, were considered to be of good quality with a low risk of bias. Quality assessments of included studies for all systematically reviewed research questions are presented in Appendix E of Technical Report Volume 2 (see the "Availability of Companion Documents" field).

Data Extraction

Data and information were extracted into evidence summary tables according to the inclusion criteria. Evidence summary tables were based on NHMRC requirements for externally developed guidelines. All articles retrieved for full text review were initially screened, critically appraised, and data extracted by one evidence reviewer. A second reviewer independently checked and reviewed all articles, data extractions, and quality assessments. Any disagreements were resolved by a third reviewer.

Extracted data and information included general study details (citation, study design, evidence level, country and setting); characteristics of study

participants; details of interventions and comparators; details of study validity, both internal (e.g., allocation and blinding) and external (applicability and generalisability); and results for outcomes specified in the inclusion criteria. Where relevant studies were identified, extracted data and information were used to construct study characteristics and results tables of included evidence for each systematically reviewed research question. Evidence summary tables for all included studies are presented in Appendix F of Technical Report Volume 2.

Assessment of the Body of Evidence

The body of evidence for each module recommendation was graded in accordance with the NHMRC framework for developing evidence-based recommendations. Assessment of the body of evidence considers the dimensions of evidence of studies relevant to that recommendation (see Table 2.4.2 of Technical Report Volume 1). A modified NHMRC evidence statement form was used with each clinical research question considered in the development of the guidelines (see Appendix 4.3 of Technical Report Volume 1). That is, a separate form was used for consolidation of the evidence (evidence statement form) and the development of recommendations (recommendation form). The decision to separate out the two components of the NHMRC evidence statement form was due to the inevitability of several evidence statement forms leading to only one recommendation. Also, the current NHMRC evidence statement form does not provide a space to capture the actual wording of evidence statements.

Before the evidence statement form was completed, included studies were critically appraised and relevant data were summarised, as described. This information was required to formulate each recommendation and determine the overall grade of the body of evidence supporting each recommendation.

The key findings from included studies were summarised as evidence statements for each systematically reviewed research question. Where required, separate evidence statements were developed for different patient populations and outcomes. CRG input helped to ensure that the size of effects and relevance of evidence were considered when developing evidence statements. Where no evidence or insufficient relevant evidence was identified, this was explained in the evidence statement.

Refer to Technical Report Volume 1 for Steps 1 and 2 in using the NHMRC evidence statement form. Completed evidence statement forms and recommendations for each research question are presented in Appendix D of Technical Report Volume 2.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Clinical/Consumer Reference Group (CRG) developed recommendations where sufficient evidence was available from the systematic review of the literature. The recommendations have been carefully worded to reflect the strength of the body of evidence. Each recommendation has been given a grade, using definitions set by the National Health and Medical Research Council (NHMRC) (see Section 2 in the original guideline document for further information on this process).

Governance Structure

A multilevel management framework was established by the National Blood Authority (NBA) to coordinate the development of the new patient blood management (PBM) guidelines. The management framework consists of:

- A Steering Committee, which was responsible for the initial development and governance of the entire project; this has now become the PBM Steering Committee, which oversees the implementation strategy for the PBM guidelines
- An Expert Working Group (EWG), responsible for providing advice on scope, clinical oversight and integration of the six modules
- CRGs – one for each of the six modules, with membership including representation from relevant colleges, societies and consumer groups, to provide expert knowledge and input
- Systematic reviewers and a technical writer, contracted by the NBA to review the literature and develop a draft of each module
- An independent systematic review expert, to provide advice and mentoring to the systematic reviewers, technical writer and CRGs; and to ensure that the development process and the guidelines produced comply with NHMRC requirements

The NBA provided the secretariat, project funding and project management. Appendix A3 in the original guideline document lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 6 of the guideline.

Formulation of Recommendations

Use of the Modified NHMRC Evidence Statement Form

Step 3. Formulation of a Recommendation Based on the Body of Evidence

Step 3 involved formulating the wording of the recommendation. This wording was intended to reflect the strength of the body evidence; that is, where the evidence base was regarded as poor or unreliable, words such as 'must' or 'should' were not used. The wording of recommendations was developed in conjunction with the CRG during meetings to review the evidence base for research questions.

Step 4. Determination of the Grade for the Recommendation

The overall grade for each recommendation was determined from a summary of the rating for each component of the body of evidence (outlined in the "Rating Scheme for the Strength of the Evidence" field). Definitions of the NHMRC grades of recommendations are presented in the "Rating Scheme for the Strength of the Recommendations" field. In accordance with the NHMRC framework, recommendations were not graded A or B unless the evidence base and consistency of evidence were both rated A or B (unless only one study was included, and consistency was rated 'NA' – in this situation the quality, size and strength of the evidence base was relied upon to grade the recommendation). The grading of recommendations was determined in conjunction with the CRG.

Developed recommendations were entered into the recommendation forms, and the corresponding evidence statement forms were noted, along with the overall grade determined in this step (see Appendix D of Technical Report Volume 2 [see the "Availability of Companion Documents" field]).

Practice Points

Practice points were developed by the CRG through a facilitated group discussion and consensus process (see Appendix 4.4 in Technical Report Volume 1 [see the "Availability of Companion Documents" field]) in the following circumstances:

- Where the underpinning evidence would have led to a Grade D evidence-based recommendation
- Where the CRG developed evidence-based recommendations graded C and above, but considered that additional information was required to guide clinical practice (wherever possible, this guidance was sourced from other evidence-based guidelines assessed to be of high quality)
- Where insufficient evidence was identified to support the development of an evidence-based recommendation

Refer to Section B4 in the original guideline document for information on development of expert opinion points.

Rating Scheme for the Strength of the Recommendations

Grade of Recommendation

Grade A: Body of evidence can be trusted to guide practice.

Grade B: Body of evidence can be trusted to guide practice in most situations.

Grade C: Body of evidence provides some support for recommendation(s) but care should be taken in its application.

Grade D: Body of evidence is weak and recommendations must be applied with caution.

Practice Point/Expert Opinion Point: The systematic review found insufficient high-quality data to produce evidence-based recommendations, but the Clinical/Consumer Reference Group (CRG) felt that clinicians require guidance to ensure good clinical practice. The CRG also developed Expert Opinion Points related to the material covered in the background questions. Both the practice points and the expert opinion points are based on consensus among the members of the CRG.

Cost Analysis

A specific literature search for economic evidence was not conducted. Any economic evidence identified in the literature that met the PICO (population, intervention, comparator and outcome) criteria was not considered.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Public Consultation

Public consultation was conducted for 8 weeks from 31 August to 23 October 2015, during which time the draft module was available on the National Blood Authority (NBA) Web site. Notification was posted in *The Weekend Australian* national newspaper, and the NBA invited a range of stakeholders, committees, working groups and interested people to provide submissions via email. A full list is detailed in the public consultation submissions report.

A formal letter advising of public consultation was sent to the organisations with a representative on the Clinical/Consumer Reference Group (CRG). An email was sent to the following:

- Members of each of the previous and current Expert Working Group (EWG), CRGs, independent systematic reviewer, Haemovigilance Advisory Committee, National Education and Training Committee and patient blood management (PBM) Steering Committee
- Relevant colleges, societies and other health organisations
- Individuals registered to receive PBM guideline updates
- Therapeutic Goods Administration
- Director General/Chief Executive/Secretary of each state, territory and health department
- Pharmaceutical Benefits Advisory Committee
- Medical Services Advisory Committee
- Australian Red Cross Blood Service
- Consumers Health Forum of Australia and the major consumer organisation in each state and territory

Thirteen submissions were received. The CRG met in November 2015 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

Finalising the Guidelines

Appraisal of Guidelines for Research and Evaluation (AGREE) II Assessment

The AGREE II instrument was developed to address the issue of variability in guideline quality and assesses the methodological rigour and transparency in which a guideline is developed. The post-public consultation version of the module was sent to two Australian reviewers, independent to the guideline development process, who used the AGREE II tool to assess the quality and usability of the module against international quality standards.

Both AGREE II assessors recommended the guideline for use, with one reviewer providing a rating of six out of seven and the other reviewer providing a rating of seven out of seven.

Additional Review

The final drafts of the module and technical reports were reviewed by a guidelines development expert (formerly a Guidelines Assessment Register consultant) to assess compliance with National Health and Medical Research Council (NHMRC) requirements for externally developed guidelines. The module and accompanying documents were then sent to the NHMRC for methodological and independent peer review on 23 December 2015.

NHMRC Approval

Approval from the NHMRC was received on 21 March 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Patient blood management (PBM) aims to improve of clinical outcomes by avoiding unnecessary exposure to blood components. It includes the three pillars of:

- Optimisation of blood volume and red cell mass
- Minimisation of blood loss
- Optimisation of the patient's tolerance of anaemia

PBM improves patient outcomes by ensuring that the focus of the patient's medical and surgical management is on improving and conserving the patient's own blood. As a consequence of the better management, patients usually require fewer transfusions of donated blood components, thus avoiding transfusion-associated complications.

Potential Harms

Traditionally, it has been assumed that blood transfusion benefits patients; however, a benefit has not been demonstrable in many clinical scenarios. In addition, evidence is accumulating that serious nonviral adverse events, such as transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI), are more common than previously thought, and that more recently identified conditions (e.g., transfusion-related immunomodulation) may cause patients harm.

The risk of transmission of infectious diseases through blood transfusion has reduced significantly in recent years, through improved manufacturing and laboratory processes. However, there is potential for transfusion of an unrecognised infectious agent.

Despite improvements in systems management, there remains a risk of transfusion-related harm due to administrative error. Such an error has the potential to result in acute haemolytic reaction from ABO incompatibility, which may be fatal.

If the patient requires therapy for anaemia, thrombocytopenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, and should:

- Take into account the full range of available therapies
- Balance the evidence for efficacy and improved clinical outcome against the risks
- Take into account patient values and choices

Table C.1 in the original guideline document summarises transfusion risks, and Table C.2 presents the Calman Chart (United Kingdom risk per one year), which may be useful to clinicians for explaining risks to patients.

Although red blood cell (RBC) transfusions may be associated with risk and morbidity, in the adult population, alternatives to transfusion such as erythropoiesis stimulating agent (ESA) therapy are not without complications.

There is the potential for toxicity if excessive iron doses are used; enteral iron can compete with zinc and copper for absorption, potentially causing clinically significant deficiencies, or can have direct adverse effects on the gut microbiome. Although evidence that iron supplementation leads to oxidative stress is inconsistent in small randomised trials, the safe upper limit of iron intake remains uncertain.

The overall intrauterine transfusion (IUT) complication rate of 3.1% includes the potential for fetal loss (1.6–1.7% per procedure). In haemolytic disease of the fetus and newborn (HDFN), each IUT can expose the mother to fetal red blood cells (RBCs), resulting in an increase in the mother's antibody titre, and potentially worsening the disease process. Before 18 weeks gestation, IUT is technically difficult. Beyond 35 weeks gestation, the risk to the fetus from IUT should be weighed against the risks from early delivery and postnatal treatment.

Contraindications

Contraindications

- Cytomegalovirus (CMV)-positive granulocyte transfusions have the potential to transmit large amounts of intracellular CMV. Leucodepletion is contraindicated (because it would deplete the granulocytes); therefore, CMV-seronegative granulocytes should be provided for recipients who are CMV seronegative or whose status is unknown.
- Permissive hypotension is contraindicated in cases of head injury.
- Platelet transfusions are not indicated in all cases of thrombocytopenia, and may be contraindicated or ineffective in certain conditions (e.g. in immune thrombocytopenia, thrombotic thrombocytopenia purpura and heparin-induced thrombocytopenia).
- Intravenous iron is contraindicated in patients who have had previous allergic reactions to iron therapy, who suffer from severe liver dysfunction, or suffer from iron overload.

Qualifying Statements

Qualifying Statements

- This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. Recommendations contained herein are based on the best available evidence published up to 12 June 2013. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.
- Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.
- This publication reflects the views of the authors and not necessarily the views of the Australian Government.
- If the patient requires therapy for anaemia, thrombocytopenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, and should:
    - Take into account the full range of available therapies
    - Balance the evidence for efficacy and improved clinical outcome against the risks
    - Take into account patient values and choices.
- In the process of obtaining informed consent, a clinician should allow the patient sufficient time to ask questions, and should answer those questions. If the patient is unable to speak or understand English, the clinician may need to involve an interpreter. In certain contexts, a trained medical interpreter may be required (rather than a family member or a friend). Written information and diagrams may be appropriate in certain circumstances to aid understanding.
- All elements of the consent process should reflect local state, territory or national requirements.

Implementation of the Guideline

Description of Implementation Strategy

Implementing, Evaluating and Maintaining the Guidelines

The National Blood Authority (NBA), in collaboration with the Steering Committee, developed a plan to guide appropriate communication on the implementation of this module. The plan identifies target audiences for the module, strategies and tools for effective implementation, communication channels and key message.

Economic issues were considered when formulating the evidence-based recommendations within each module, and these recommendations will have cost implications. Recommendation 2 is likely to change current practice; however, the resource implications of the additional magnetic resonance imaging (MRI) and transcranial Doppler (TCD) screening for sickle cell disease (SCD) are expected to be low, given the size of the relevant population and the small number of scans required. The NBA, together with the Jurisdictional Blood Committee and key stakeholders, developed the *National Patient Blood Management Guidelines Implementation Strategy 2013–17* to facilitate uptake of the guidelines.

The implementation strategy includes the development of tools to support the introduction of patient blood management (PBM) practices in the clinical setting. The tools are being developed with the help of a network of clinicians with an interest in PBM. The NBA has also funded the

development of online courses within the BloodSafe eLearning Australia program (e.g., on iron deficiency anaemia [IDA], PBM, critical bleeding and perioperative). In addition, the NBA, in collaboration with the Australian Commission on Safety and Quality in Health Care (ACSQHC), has developed a hospital guide to support the implementation of the National Safety and Quality Health Service Standards. The guide provides links to the PBM guidelines and tools, and the BloodSafe eLearning Australia courses. These resources provide tools to support uptake of the recommendations in this module.

The *National Blood Sector Education and Training Strategy 2013-16* outlines a plan to work with current education and training providers to address the growing demand for high-quality, well-tailored education, training and health-promotion materials to support the implementation of evidence-based practice and attainment of health service accreditation under the new *National Safety and Quality Health Service (NSQHS) Standards*. The National Education and Training (NEAT) Committee has been established to support the implementation of the strategy. The NBA will engage with key stakeholders in the sector and enter into collaborations, joint arrangements and outsourcing to meet the key strategies identified for 2013–16.

Continued re-evaluation of the guidelines is necessary to reduce variation in practice patterns, support appropriate use of blood component therapy and reduce inappropriate exposure of patients to blood components. A plan was designed to evaluate implementation of the six modules of the guidelines and to determine:

- The extent to which the guidelines influence changes in clinical practice and health outcomes
- What factors (if any) contribute to noncompliance with the guidelines

A literature review and interviews were conducted with experts in guideline development in Australia and internationally. The recommendations from the evaluation report were used to investigate and pilot more time-efficient and cost-effective methods of guideline development.

The NBA has surveyed users of the PBM guidelines and is monitoring emerging technologies. It is also working with the National Health and Medical Research Council (NHMRC), Cochrane Collaboration and other clinical research groups who have published systematic reviews relevant to the topic to pilot more streamlined processes, in a targeted update of *Module 1 – Critical Bleeding/Massive Transfusion* in 2015–16.

Implementation of Guidelines Recommendations

The NHMRC framework directs that guidelines implementation should be considered at the same time as recommendations are formulated. The recommendation form contains questions related to the implementation of each module (Appendix 4.3 in Technical Report Volume 1 [see the "Availability of Companion Documents" field]). These are:

- Will this recommendation result in changes in usual care?
- Are there any resource implications associated with implementing this recommendation?
- Will the implementation of this recommendation require changes in the way care is currently organised?
- Is the guidelines development group aware of any barriers to the implementation of this recommendation?

This section of the recommendation form was completed in consultation with the Clinical/Consumer Reference Group (CRG) when each recommendation was formulated and graded. Implementation issues are recorded in the recommendation forms presented in Appendix D of Technical Report Volume 2 (see the "Availability of Companion Documents" field).

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Blood Authority (NBA). Patient blood management guidelines: module 6 - neonatal and paediatrics. Canberra ACT (Australia): National Blood Authority (NBA); 2016. 298 p. [401 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016

Guideline Developer(s)

National Blood Authority - National Government Agency [Non-U.S.]

Source(s) of Funding

Funding, secretariat and project management was provided by the National Blood Authority Australia. The development of the final recommendations has not been influenced by the views or interests of the funding body.

Guideline Committee

Steering Committee

Expert Working Group

Composition of Group That Authored the Guideline

Steering Committee: A/Prof Lilon Bandler, Independent clinical expert, general practitioner; Ms Karen Carey, Consumers Health Forum, consumer representative; Dr James Daly, Clinical and laboratory haematologist, Australian & New Zealand Society of Blood Transfusion; Dr Steve Flecknoe-Brown, Independent clinical expert, senior consultant physician and haematologist; Ms Trudi Gallagher, Independent clinical expert, clinical nurse consultant and jurisdictional PBM coordinator; Professor James Isbister (*Chair*), Independent clinical academic expert and honorary haematology and transfusion medicine consultant; Dr Kerry Gunn, Specialist anaesthetist, PBM expert in anaesthetics; Ms Kathy Meleady Director, Commonwealth Programs, Australian Commission on Safety and Quality in Health Care; Ms Bronwyn Pearce, Independent clinical expert, clinical nurse consultant; Dr Beverley Rowbotham, Independent clinical expert, haematologist, private pathology; Dr Rashmi Sharma, Independent clinical expert, general practitioner; Ms Tracey Spigiel, Nurse, Australian Red Cross Blood Service; Dr Amanda Thomson, Independent clinical expert, haematologist; Dr Simon Towler, Intensive care specialist, PBM expert and immediate past Chair

Expert Working Group: A/Prof Mark Dean, Royal Australasian College of Physicians, and Haematology Society of Australia & New Zealand; A/Prof Craig French, Australian & New Zealand Intensive Care Society, and College of Intensive Care Medicine of Australia and New Zealand; A/Prof Helen Liley, Royal Australasian College of Physicians (Paediatrics and Child Health Division), and Perinatal Society of Australia & New Zealand; A/Prof Larry McNicol, Australian and New Zealand College of Anaesthetists; Dr Helen Savoia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; Dr Amanda Thomson, Australian & New Zealand Society of Blood Transfusion

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Financial Disclosures/Conflicts of Interest

All members of the Patient Blood Management (PBM) Steering Committee, Clinical/Consumer Reference Group (CRG), Expert Working Group (EWG) and systematic review team declared any interests before starting work on the guidelines. New declarations were required to be declared to the Chair before the start of each meeting as a standing agenda item on each day of a meeting. The National Blood Authority (NBA) keeps a register of all declared interests. If an interest is declared, and the Chair decides that it should be considered by the CRG, the CRG decides by consensus whether it affects the proceedings. If the interest is considered to be competing or in conflict, the Chair directly manages the participation of that member in relation to discussions and decisions pertaining to the declared interest.

Unlike the pecuniary interests declared by CRG members that are published in the PBM guidelines, declarations of a more personal nature can be made in confidence to the NBA. These declarations are forwarded to the Chair, and this is followed by a discussion with the CRG member, who is required to sign and agree to the enactment of an action management plan. At this time, the Chair determines whether the declaration:

a. Is an actual or perceived conflict of interest
b. Requires disclosure to the other members
c. Can be managed without jeopardising the rigorous methodology process and accurate reporting of the evidence in the guidelines
d. Requires the member to be excluded from certain or all discussions
e. Requires the member to stand down from their role on the CRG

The recommendation of the Chair is forwarded to the NBA General Manager for final decision. Any and all perceived or actual conflict of interest declarations made in confidence and subsequent management action plans are treated as sensitive personal information and, as such, are not made

public and are not published in the guideline.

See Appendix B in the original guideline document for declarations made during the guideline development process.

The Chair considered these declarations and determined that all except one did not constitute a conflict of interest. In that instance, a management action plan was established. The Chair's declarations were reviewed by the co-Chairs of the EWG and were not considered a conflict of interest. None of the NBA and Optum staff had any declarations.

Guideline Endorser(s)

Australasian College for Emergency Medicine - Medical Specialty Society

Australasian Society for Emergency Medicine - Medical Specialty Society

Australian and New Zealand Society of Blood Transfusion - Medical Specialty Society

Australian College of Children and Young People's Nurses - Professional Association

Australian College of Critical Care Nurses - Professional Association

Australian College of Rural and Remote Medicine - Professional Association

Australian Red Cross Blood Service - Nonprofit Organization

College of Intensive Care Medicine of Australia and New Zealand - Medical Specialty Society

Royal Australasian College of Surgeons - Professional Association

Royal College of Pathologists of Australasia - Professional Association

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Blood Authority (NBA) Web site .

Availability of Companion Documents

The following are available:

- Patient blood management guidelines: module 6 - neonatal and paediatrics. Quick reference guide. Canberra ACT (Australia): National Blood Authority; 2016. 85 p. Available from the National Blood Authority (NBA) Web site .
- Patient blood management guidelines: module 6 - neonatal and paediatrics. Technical report. Volume 1. Review of the evidence. Canberra ACT (Australia): National Blood Authority; 2015 Nov. 629 p. from the NBA Web site .
- Patient blood management guidelines: module 6 - neonatal and paediatrics. Technical report. Volume 2. Appendixes. Canberra ACT (Australia): National Blood Authority; 2015 Nov. 775 p. Available from the NBA Web site .

Additional implementation resources, including the haemoglobin assessment and optimisation template (Appendix H) and the Critical Bleeding Protocol (Appendix K), are available from the NBA Web site . Instructions on how to add the guidelines to your mobile device are available from the NBA Web site .

Patient Resources

Various tools and resources to support patients in patient blood management decision making are available on the National Blood Authority (NBA) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on December 7, 2016. The information was verified by the guideline developer on December 15, 2016.

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ISBN 978-0-9944061-0-1 (hard copy)

ISBN 978-0-9944061-2-5 (electronic copy)

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