Patient Blood Management

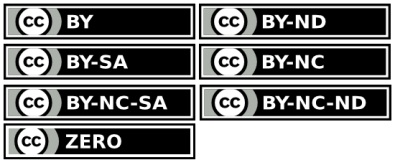
Guidelines: Module 6

Neonatal and paediatrics

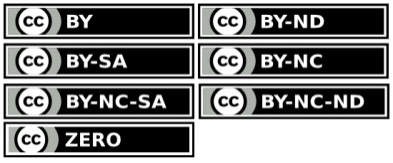
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Disclaimer

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.

**Publication approval**

[Insert NHMRC LOGO]

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on [Day Month Year TBC by NBA], under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health-care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

**Patient Blood Management Guidelines:**

**Module 6 – Neonatal and Paediatrics**

Development of this module was achieved through clinical input and expertise of representatives from the colleges and societies listed below, a patient blood management consultant and an independent consumer advocate (see Appendix A).

**Australian and New Zealand Children’s Haematology/Oncology Group   
Australian and New Zealand Intensive Care Society**

**Australian & New Zealand Society of Blood Transfusion**

**Australian College of Children and Young People’s Nurses**

**College of Intensive Care Medicine of Australia and New Zealand**

**Haematology Society of Australia & New Zealand**

**Perinatal Society of Australia and New Zealand**

**Royal Australian and New Zealand College of Obstetricians and Gynaecologists**

**Royal Australasian College of Surgeons**

**Royal College of Pathologists of Australasia**

**Thalassaemia Australia**

The National Blood Authority gratefully acknowledges these contributions. College and society endorsement of this module can be found at [www.blood.gov.au](http://www.blood.gov.au)



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# Abbreviations and acronyms

|  |  |
| --- | --- |
| ACSQHC | Australian Commission on Safety and Quality in Health Care |
| AGREE | Appraisal of Guidelines for Research & Evaluation |
| AHCDO | Australian Haemophilia Centre Directors' Organisation |
| AHMAC | Australian Health Ministers’ Advisory Committee |
| AI | adequate intake |
| ANH | acute normovolaemic haemodilution |
| ANZSBT | Australian & New Zealand Society of Blood Transfusion |
| ASBT | Australasian Society of Blood Transfusion |
| BPD  CBP | bronchopulmonary dysplasia  critical bleeding protocol |
| CKD | chronic kidney disease |
| CMV | cytomegalovirus |
| COAG | Council of Australian Governments |
| CPB | cardiopulmonary bypass |
| CRG | Clinical/Consumer Reference Group |
| EACA | epsilon-aminocaproic acid |
| EBV | estimated blood volume |
| ECLS | extracorporeal life support |
| ECMO | extracorporeal membrane oxygenation |
| ENT | ear, nose and throat |
| EOP | expert opinion point |
| ES | evidence statement |
| ESA | erythropoiesis stimulating agent |
| ET | exchange transfusion |
| EWG | Expert Working Group |
| FBS | fetal blood sampling |
| FFP | fresh frozen plasma |
| FNAIT | fetal and neonatal alloimmune thrombocytopaenia |
| Hb | haemoglobin |
| Hct | haematocrit |
| HDFN | haemolytic disease of the fetus and newborn |
| HIV | human immunodeficiency virus |
| HLA | human leucocyte antigen |
| HPA | human platelet antigen |
| ICH | intracranial haemorrhage |
| ICU | intensive care unit |
| IDA | iron deficiency anaemia |
| IgG | immunoglobulin G |
| IM | intramuscular |
| INR | international normalised ratio |
| IUT | intrauterine transfusion |
| IV | intravenous |
| IVH | intraventricular haemorrhage |
| IVIg | intravenous immunoglobulin |
| JBC | Jurisdictional Blood Committee |
| KDIGO | Kidney Disease Improving Global Outcomes |
| MCA | middle cerebral artery |
| MODS | multiple organ dysfunction syndrome |
| MRI | magnetic resonance imaging |
| NBA | National Blood Authority |
| NEC | necrotising enterocolitis |
| NHMRC | National Health and Medical Research Council |
| NICE | National Institute for Health and Care Excellence |
| NICU | neonatal intensive care unit |
| NIH | National Institutes of Health |
| NNNI | Northern Neonatal Nursing Initiative |
| NZBS | New Zealand Blood Service |
| PBM | patient blood management |
| PCC | prothrombin complex concentrate |
| PICO | population, intervention, comparator and outcome |
| PICU | paediatric intensive care unit |
| POC | point of care |
| PP | practice point |
| PSV | peak systolic velocity |
| R | recommendation |
| RBC | red blood cell |
| RCT | randomised controlled trial |
| RDI | recommended daily intake |
| rFVIIa | recombinant activated factor VII |
| rHuEPO | recombinant human erythropoietin |
| RNI | recommended nutrient intake |
| ROP | retinopathy of prematurity |
| ROTEM | rotational thromboelastometry |
| SCD | sickle cell disease |
| SCID | severe combined immunodeficiency |
| TACO | transfusion-associated circulatory overload |
| TAGVHD | transfusion-associated graft-versus-host disease |
| TCD | transcranial Doppler |
| TEG | thromboelastography |
| TGA | Therapeutic Goods Administration |
| THA | topical haemostatic agent |
| TRALI | transfusion-related acute lung injury |
| TWiTCH | TCD With Transfusions Changing to Hydroxyurea |
| TXA | tranexamic acid |
| UK | United Kingdom |
| USA | United States of America |
| VKA | vitamin K antagonist |

Contents

Abbreviations and acronyms i

Plain English summary 1

Summary of recommendations, practice points and expert opinion points 2

1 Introduction 15

1.1 Development of the guidelines 15

1.1.1 Clinical need for these guidelines 15

1.2 Structure of the document and related materials 16

1.2.1 The document 16

1.2.2 Related materials 17

2 Methods 19

2.1 Clinical research questions 19

2.1.1 Question development summary 19

2.1.2 Background material 19

2.2 Review and research 20

2.2.1 Systematic review process 20

2.2.2 Literature search dates 20

2.2.3 Inclusion and exclusion criteria 21

2.3 Development of evidence statements, recommendations and practice points 21

3 Clinical guidance 23

3.1 Introduction 23

3.1.1 Purpose and audience 23

3.1.2 Scope 23

3.1.3 Patient population and setting 23

3.1.4 Formation of evidence statements 24

3.2 Effect of RBC transfusion on outcomes 25

3.2.1 Neonatal patients – effect of RBC transfusion on patient outcomes 25

3.2.2 Infants, children and adolescents – effect of RBC transfusion on patient outcomes 31

3.2.3 Medical: neonatal and paediatric patients with SCD – effect of RBC transfusion on patient outcomes 34

3.2.4 Medical: neonatal and paediatric patients with beta thalassaemia – effect of RBC transfusion on patient outcomes 37

3.2.5 Medical: paediatric patients with cancer – effect of RBC transfusion on patient outcomes 38

3.2.6 Neonatal and paediatric patients undergoing surgery – effect of RBC transfusion on patient outcomes 40

3.2.7 Critically ill neonatal and paediatric patients – effect of RBC transfusion on patient outcomes 44

3.3 Effect of non-transfusion interventions to increase Hb concentration on outcomes 46

3.3.1 Preterm and low birth weight infants – effect of ESAs (with or without iron) on outcomes 47

3.3.2 Preterm and low birth weight infants – effect of oral and/or parenteral iron on outcomes 50

3.3.3 Infants, children and adolescents at risk of anaemia – effect of ESAs (with or without iron) on outcomes 52

3.3.4 Infants, children and adolescents at risk of anaemia – effect of oral and/or parenteral iron on outcomes 53

3.3.5 Medical: neonatal and paediatric patients with cancer – effect of ESAs (with or without iron) on outcomes 55

3.3.7 Medical: neonatal and paediatric patients with kidney disease – effects of ESAs (with or without iron) on outcomes 58

3.3.8 Medical: neonatal and paediatric patients with kidney disease – effect of oral and/or parenteral iron on outcomes 61

3.3.9 Medical: neonatal and paediatric patients with SCD – effect of hydroxyurea 63

3.3.10 Medical: neonatal and paediatric patients undergoing surgery – general 65

3.3.11 Medical: neonatal and paediatric patients undergoing surgery – effect of ESAs (without or without iron) on outcomes 66

3.3.12 Medical: neonatal and paediatric patients undergoing surgery – effect of oral and/or parenteral iron on outcomes 68

3.3.12 Critically ill term and near term neonatal patients and paediatric patients – general 69

3.3.13 Critically ill term and near term neonatal patients and paediatric and patients – effect of ESAs, with or without iron, on outcomes 69

3.3.14 Critically ill term and near term neonatal patients and paediatric patients – effect of oral and/or parenteral iron, on outcomes 71

3.4 Effect of blood components on outcomes 71

3.4.1 Preterm and low birth weight infants – effects of FFP on outcomes 73

3.4.2 Preterm and low birth weight infants – effects of platelet transfusion on outcomes 75

3.4.3 Preterm and low birth weight infants – effects of platelet transfusion using a different transfusion strategy on outcomes 77

3.4.4 Paediatric patients with cancer – effects of platelet transfusion on outcomes 78

3.4.5 Neonatal and paediatric patients undergoing surgery – effects of FFP on outcomes 81

3.4.6 Neonatal and paediatric patients undergoing surgery – effects of cryoprecipitate on outcomes 84

3.4.7 Neonatal and paediatric patients undergoing surgery – effects of platelets on outcomes 86

3.4.8 Neonatal and paediatric patients undergoing surgery – effects of fibrinogen concentrate on outcomes 88

3.4.9 Neonatal and paediatric patients undergoing surgery – effects of use of a different fibrinogen strategy on outcomes 90

3.4.10 Neonatal and paediatric patients undergoing surgery – effects of combination therapy on outcomes 92

3.4.11 Critically ill neonatal and paediatric patients – effects of FFP on outcomes 93

3.4.12 Critically ill neonatal and paediatric patients – effects of cryoprecipitate on outcomes 95

3.4.13 Critically ill neonatal and paediatric patients – effects of platelets on outcomes 97

3.4.14 Critically ill neonatal and paediatric patients – effects of fibrinogen concentrate on outcomes 99

3.4.15 Critically ill neonatal and paediatric patients – effects of combination therapy on outcomes 101

3.5 Use of blood conservation strategies 102

3.5.1 Preterm and term infants – effects of placental transfusion on outcomes 104

3.5.2 Preterm and term infants – effects of IVIg for haemolytic disease on outcomes 106

3.5.3 Neonatal and paediatric patients undergoing surgery – effects of prevention of hypothermia on outcomes 108

3.5.4 Neonatal and paediatric patients undergoing surgery – effects of prevention of controlled induced hypotension on outcomes 110

3.5.5 Neonatal and paediatric patients undergoing surgery – effects of ANH on outcomes 112

3.5.6 Neonatal and paediatric patients undergoing surgery – effects of intraoperative cell salvage on outcomes 113

3.5.7 Neonatal and paediatric patients undergoing surgery – effects of viscoelastometric POC testing on outcomes 115

3.5.8 Neonatal and paediatric patients undergoing surgery – effects of antifibrinolytics on outcomes 116

3.5.9 Neonatal and paediatric patients undergoing surgery – effects of rFVIIa on outcomes 126

3.5.10 Neonatal and paediatric patients undergoing surgery – effects of miniaturised CPB systems on outcomes 128

3.5.11 Critically ill neonatal and paediatric patients – effects of rFVIIa on outcomes 129

3.5.12 Critically ill neonatal and paediatric patients – effects of viscoelastometric POC testing on outcomes 130

3.6 Considerations for Aboriginal and Torres Strait Islander neonates and children 131

3.6.1 Key points 131

4 Background questions 133

4.1 Selection of blood products 134

4.1.1 Use of ‘fresh’ RBCs in fetal, neonatal or paediatric patients 134

4.1.2 Kell antigen system 135

4.1.3 Use of irradiated cellular blood products in neonates and children 135

4.1.4 Use of CMV-negative blood products 137

4.1.5 Use of human platelet antigen-matched platelets 139

4.1.6 Use of HLA-matched platelets 140

4.1.7 Washed RBCs 141

4.2 The need for neonatal transfusion 142

4.2.1 Intrauterine fetal blood component transfusion 142

4.3 Non-pharmacologic blood conservation strategies 144

4.3.1 Introduction 144

4.3.2 Early removal of sampling lines 144

4.3.3 Avoiding excess phlebotomy volumes 144

4.3.4 As-needed or rationalisation of blood sampling 144

4.3.5 Replacement or avoidance of discard or void volumes in sampling lines 145

4.3.6 Non-invasive techniques for testing of Hb, blood gases and other analytes 145

4.4 Strategies to minimise blood loss in cardiac surgery 145

4.4.1 Prothrombin complex concentrate 146

4.4.2 Topical haemostatic agents 146

4.5 Iron Deficiency Anaemia 147

4.5.1 Iron requirements in infants and children 148

4.5.2 Iron deficiency in infants and children 149

4.5.3 Diagnosis of IDA 149

4.5.4 Iron therapy in infants, children and adolescents 149

4.5.5 Iron toxicity 152

4.6 Critical bleeding 152

5 Future directions 155

5.1 Evidence gaps and areas for future research 155

6 Implementing, evaluating and maintaining the guidelines 158

6.1 Implementation strategies 158

6.2 Endorsement 159

6.3 Scheduled review and update 159

Appendix A Governance 161

Appendix B Process report 169

Appendix C Transfusion risks in the context of patient blood management 175

Appendix D Blood sectors 177

Appendix E Product information 181

Appendix F RBC transfusions in preterm infants 182

Appendix G Paediatric haemoglobin assessment and optimisation template 183

Appendix H Tranexamic acid dosing guidance 186

Appendix I Intravenous Iron 187

Appendix J Transfusion volume calculation for neonates, infants and small children 191

Appendix K Critical bleeding protocol 193

References 196

Tables

Table 1.1 Phases of development of guideline modules 16

Table 2.1 Body of evidence matrix 22

Table 2.2 Definitions of NHMRC grades for recommendations 22

Table 3.1 Structure of evidence statements 24

Table 3.2 Description of interventions 24

Table 4.1 Indications for irradiation of cellular products 136

Table 4.2 Products for IUT 143

Table 4.3 Iron requirements in neonates and infants 149

Table 4.4 Quick dose reference to provide 3 mg/kg/day (for severe IDA, consider 6 mg/kg/day) 150

Table 4.5 Paediatric appropriate iron formulations in Australia 150

Table C.1 Transfusion risks 176

Table C.2 Calman Charta (United Kingdom risk per 1 year) 176

Table F.1 Haemoglobin threshold for preterm infants 182

Table H1 Guidance on tranexamic dosing in surgical paediatric patients other than cardiac 186

Table I-1 Total dose (mg of IV iron carboxymaltose) based on Hb concentration and body weight 189

Table I-2 Dose (ml of IV iron sucrose) based on Hb concentration and body weight 189

Table I-3 Dose (ml of IV iron polymaltose) based on Hb concentration and body weight 190

Table J.1 Hct values 191

Table J.2 Approximate Hb increments that can be expected for transfusion 192

Figure

[Figure A1 Management framework for development of the guidelines 162](#_Toc427758407)

# Plain English summary

This document, *Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics*,is the sixth in a series of six modules that focus on evidence-based patient blood management. The other five modules are *Critical Bleeding/Massive Transfusion*,[1](#_ENREF_1) *Perioperative*,[2](#_ENREF_2) *Medical*,[3](#_ENREF_3) *Critical Care*[*4*](#_ENREF_4)and *Obstetrics and Maternity*.[5](#_ENREF_5) Together, Module 2 (*Perioperative*)[2](#_ENREF_2) and Module 3 (*Medical*)[3](#_ENREF_3) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*[6](#_ENREF_6) (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

This document was developed by a Clinical/Consumer Reference Group (CRG) representing specialist colleges, organisations and societies, with the active participation of the clinical community.

This plain English summary includes a summary of:

the *recommendations* that were developed by the CRG, based on evidence from a systematic review

the *practice points* that were developed by the CRG through consensus decision making

the *expert opinion points* that were developed by the CRG through consensus decision making.

Details of the systematic reviews used in the development of this module are given in the two-volume technical report that accompanies this document.[7-8](#_ENREF_7)

Materials relevant to consumers and to clinicians working in neonatal and paediatric services will be developed to accompany this module; these materials will be available online and in print.

**RECOMMENDATION**

**BASED ON EVIDENCE**

**FROM THE**

**SYSTEMATIC REVIEW**

**EXPERT OPINION POINT**

YES

**PRACTICE POINT**

**BASED ON CONSENSUS OF THE CRG**

**SUFFICIENT HIGH- QUALITY DATA**

*YES*

*NO*

*YES*

*NO*

*NO*

**NO STATEMENT MADE**

## Summary of recommendations, practice points and expert opinion points

The 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 the following definitions, set by the NHMRC:

*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.

The CRG developed practice points where 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.

| **Identifier and grade** | **Guidance – recommendations, practice points and expert opinion points** | **Relevant section of document** |
| --- | --- | --- |
| **RBC transfusion** | | |
| R1 (Grade C) | In paediatric patients, including those who are critically ill, a restrictive transfusion strategy should be employed.a Higher Hb thresholds are appropriate in very low birth weight neonates.b  a See PP6 for guidance on a restrictive transfusion strategy. b See PP2 and PP3 for guidance for preterm neonates. | 3.2.1, 3.2.2, 3.2.6, 3.2.7 |
| PP1 | In neonatal and paediatric patients, the decision to give a RBC transfusion should not be dictated by a Hb concentration alone.a 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.  a See PP1 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.2.1, 3.2.6 |
| PP2 | Neonatal units should use a procedural guidelinea for RBC transfusion in preterm infants that includes the following:   * age of infant * Hb or Hct * level of respiratory support * ongoing or anticipated red cell loss * nutritional status.   a See Appendix F (*RBC transfusions in preterm infants*). | 3.2.1 |
| PP3 | In preterm infants requiring transfusion, there is insufficient evidence to support or refute the use of either a restrictive or liberal RBC transfusion strategy. | 3.2.1 |
| PP4 | In neonatal patients, calculate transfusion volume (mL) based on weight and desired Hb increment. a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). | 3.2.1 |
| PP5 | For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:   * 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. | 3.2.2, 3.2.5, 3.2.6 |
| PP6 | In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensusa 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.   a See PP3 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.2.2, 3.2.5, 3.2.6 |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). | 3.2.2, 3.2.5, 3.2.6 |
| PP9 | 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.  See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) | 3.2.2, 3.2.5, 3.2.6 |
| PP10 | 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. | 3.2.2 |
| PP12 | In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.a A template protocol is provided within the module.b  a The use of the word ‘protocol’ is not strictly prescriptive.  b The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. | 3.2.2, 3.2.6, 3.2.7 |
| EOP5 | The routine use of ‘fresh’ (<7 days) RBCs is not advocated for routine use, but may be considered in the following clinical situations:   * IUT (<5 days, if available) * large-volume transfusion (>25 mL/kg) * exchange transfusion * cardiac surgery * transfusion-dependent chronic anaemia (RBCs <14 days) * where irradiated blood products are used. | 4.1.1 |
| EOP6 | Where possible, K-negative RBC should be selected for transfusion for all females of childbearing potential who are K negative or whose K antigen status is unknown. This includes fetal transfusion. | 4.1.2 |
| EOP7 | In both male and female chronically transfused patients, RBC should be selected to match RhD, RhC/c, RhE/e and K antigen status. | 4.1.2 |
| R2 (Grade A) | In children and adolescents with SCD who have been assessed to be at increased risk of stroke,a ongoing prophylactic RBC transfusions are recommended because they reduce stroke occurrence.b  a Assessed by TCD ultrasonography[9](#_ENREF_9) and MRI.[10](#_ENREF_10) b See PP11 for methods of assessment. | 3.2.3 |
| PP7 | 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.a  a See PP23 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.2.3 |
| PP11 | Children and adolescents with SCD should be assessed for stroke risk using both TCD ultrasonography[9](#_ENREF_9) and MRI.[10](#_ENREF_10) | 3.2.3 |
| **Hydroxyurea** | | |
| R4 (Grade B) | In paediatric patients with SCD, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.a, b  a Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke.  b See R1 and PP21. | 3.3.9 |
| PP22 | In paediatric patients over 9 months of age with SCD, hydroxyurea may be used to reduce vaso-occlusive pain crises and acute chest syndromes. | 3.3.9 |
| **ESAs** | | |
| R3 (Grade C) | In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised. | 3.3.1 |
| R5  (Grade C) | In surgical paediatric patients with or at risk of IDA, preoperative iron therapy is recommended.a  a See R4 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) | 3.3.12 |
| PP17 | 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  a See R2 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.3.5 |
| PP18 | In paediatric patients with CKD, 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  a See R4 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) b The KDIGO guidelines[11](#_ENREF_11) 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. c The NICE guidelines[12](#_ENREF_12) 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). | 3.3.7 |
| PP19 | In adult patients with CKD, 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  a See R6 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.3.7 |
| PP20 | ESA use is less effective in patients with CKD who have absolute or functional iron deficiency.a  a See PP13 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.3.7 |
| PP21 | Where ESAs are indicated for the treatment or prevention of anaemia in neonatal and paediatric patients, they should be combined with iron therapy. | 3.3.7 |
| PP25 | 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. | 3.3.11 |
| PP26 | In critically ill paediatric patients with anaemia, ESAs should not be *routinely* used.a  a This point is based on the lack of effect of ESAs on mortality in critically ill adult patients. See R2 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[4](#_ENREF_4) | 3.3.13 |
| **Oral and/or parenteral iron** | | |
| PP13 | Preterm and low birth weight infants should receive iron supplementation as necessary to achieve the RNI. However, routine supplementation in excess of the RNI, to reduce transfusion incidence, is not supported. | 3.3.2 |
| PP14 | Infants and children should receive sufficient dietary iron to achieve the AI or RDI. If the AI or RDI cannot be met by dietary means, iron supplementation is advised. | 3.3.4 |
| PP15 | Infants and children in populations at high riska of iron deficiency should be screened for this condition.b  a See Domellof et al (2014)[13](#_ENREF_13) and Pottie et al (2011)[14](#_ENREF_14) b See Section 3.6. | 3.3.4 |
| PP16 | Infants and children with iron deficiency should be treated with iron supplements and dietary modifications. | 3.3.4 |
| PP23 | In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiencya should be identified, evaluated and managed to minimise RBC transfusion.b  a Iron deficiency can be present with a normal Hb.  b See Appendix G (*Paediatric haemoglobin assessment and optimisation template*) for further information on the optimal dosing strategy. | 3.3.12 |
| PP24 | To implement PP23, 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. | 3.3.12 |
| PP27 | Critically ill paediatric patients should receive iron supplementation as necessary to achieve the RNI. | 3.3.14 |
| EOP30 | From 6 months of age, all infants and children should receive iron-rich foods. | 4.5.5 |
| EOP31 | Cow’s milk should not be given to infants before 12 months of age; from 12 months of age, cow’s milk intake should not exceed 500 mL per day. | 4.5.5 |
| EOP32 | IV iron should be administered according to a protocol relevant to the specific product being used:  IV iron formulations have different iron concentrations, maximum doses, dilutions and rates of administration; they are not interchangeable with regard to dose, dilution and rates of administration  IV iron formulations should only ever be administered in an appropriate health-care setting with medical personnel and resuscitation facilities on site. | 4.5.5 |
| **FFP, cryoprecipitate, fibrinogen concentrate and platelets** | | |
| R6 (Grade C) | 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. | 3.4.5 |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. | 3.4.1–3.4.15 |
| PP29 | For guidance on the use of FFP in specific patient groups, refer to:a  *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)*[1](#_ENREF_1)  *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*[2](#_ENREF_2)  *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*[15](#_ENREF_15)  AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au)  *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*.[16](#_ENREF_16)  a See PP17 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.4.4, 3.4.5, 3.4.11 |
| PP30 | 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 × 109/L in the absence of risk factors, and at <20 × 109/L in the presence of risk factors (e.g. fever, minor bleeding).  a See R8 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | 3.4.4 |
| EOP1 | 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 POC or laboratory testing. | 3.4.5 |
| EOP2 | 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 groups.a  a The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. | 3.4.6 |
| EOP3 | In general, neonatal and paediatric patients with a platelet count ≥ 50 × 109/L *or* an INR ≤2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts and higher INRs may be tolerated.a  a See PP17 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) | 3.4.7 |
| **Irradiated blood products** | | |
| EOP8 | Irradiated cellular blood products (RBCs and platelets) are used to prevent TAGVHD, and are indicated for:  IUT, and recipients of prior IUT up to 6 months of age  suspected or known severe congenital T-cell immunodeficiency (e.g. SCID)  severe acquired T-cell dysfunction, related to either disease or drug therapy (see published guidelines[17-18](#_ENREF_17))  HLA-matched cellular blood products (RBCs, platelets and granulocytes).  They may also be considered for:  neonatal exchange transfusion, provided this does not unduly delay transfusion  very low birth weight neonates, especially extremely preterm (<28 weeks) or extremely low birth weight infants  certain patients undergoing chemotherapy (depending on degree of immunosuppression). | 4.1.3 |
| EOP9 | Stem cells must not be irradiated. | 4.1.3 |
| EOP10 | Hyperkalaemia may occur when large volumes of irradiated blood are transfused. In patients at risk, irradiated blood should be as fresh as possible (<7 days) and used within 24 hours of irradiation. | 4.1.3 |
| EOP11 | Patients at high risk of TAGVHD (such as those with T-cell immunodeficiency) should be given clear written information (e.g. in the form of patient information leaflets or cards). Alerts should be incorporated in the hospital medical record and the blood bank or pharmacy IT system. | 4.13 |
| **Placental transfusion** | | |
| PP31 | In preterm infants, deferring cord clamping for between 30 seconds and 3 minutes may reduce transfusion volume and incidence, and incidence of IVH. 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. | 3.5.1 |
| PP32 | In term infants, deferring cord clamping for at least 1 minute is likely to reduce the risk of iron deficiency at 3–6 months. This intervention should be considered in infants who do not require active resuscitation, provided that access to phototherapy for jaundice is available.a  a See McDonald et al (2013).[19](#_ENREF_19) | 3.5.1 |
| **IVIg** | | |
| R7  (Grade B) | In infants with HDFN, the *routine* use of IVIg is not recommended. | 3.5.2 |
| PP33 | Infants at risk of HDFN should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. | 3.5.2 |
| EOP4 | In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. | 3.5.2 |
| **Measures to prevent hypothermia** | | |
| R8  (Grade B) | In paediatric patients undergoing surgery, measures to prevent hypothermia should be used.a  a See R12 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) | 3.5.3 |
| **Antifibrinolytics** | | |
| R9  (Grade B) | In paediatric patients undergoing cardiac surgery with CPB, the routine use of antifibrinolytics is recommended.a  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. | 3.5.8 |
| R10  (Grade C) | In paediatric patients undergoing surgery for scoliosis in whom substantial blood loss is anticipated, the use of antifibrinolytics should be considered.  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. | 3.5.8 |
| R11  (Grade C) | In paediatric patients undergoing craniofacial surgery in whom substantial blood loss is anticipated, the use of antifibrinolytics should be considered.  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. | 3.5.8 |
| PP37 | In acutely bleeding critically ill paediatric trauma patients, TXA should be administered within 3 hours of injury.a  a See R3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*[4](#_ENREF_4) | 3.5.8 |
| PP38 | In paediatric trauma patients aged under 12 years, a tranexemic 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.a  a See the template given in Appendix K (*Critical bleeding protocol*), which is intended for local adaptation. | 3.5.8 |
| **rFVIIa** | | |
| R12  (Grade C) | In paediatric patients undergoing cardiac surgery with CPB, the *routine* use of rFVIIa is not recommended. | 3.5.9 |
| **ANH** | | |
| PP34 | In paediatric patients, ANH has not been shown to reduce transfusion or improve clinical outcomes. However, if ANH 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. | 3.3.5 |
| **Intraoperative cell salvage** | | |
| PP35 | In paediatric patients undergoing cardiac surgery with CPB, 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. | 3.5.6 |
| **Viscoelastometric POC testing** | | |
| PP36 | In paediatric patients undergoing cardiac surgery with CPB, viscoelastometric POC testing may be considered. | 3.5.7 |
| **CMV-negative cellular products** | | |
| EOP12 | CMV-negative products may be considered in the following situations:  IUT  preterm neonates (up to 28 days after expected date of delivery)  patients with SCID who are CMV negative  stem cell transplantation where both donor and recipient are known to be CMV negative  granulocyte transfusions for recipients who are CMV seronegative, or whose status is unknown.  CMV-negative products are generally not required in other clinical settings. | 4.1.4 |
| EOP13 | In urgent situations, if CMV-seronegative blood components are not available, CMV-unscreened leucodepleted components should be used to avoid delays. | 4.1.4 |
| **HPA-matched platelets** | | |
| EOP14 | For neonates with known or suspected FNAIT, urgent platelet transfusion should be given if platelets are below 30 × 109/L in a term infant or below 50 × 109/L in a preterm infant, even in the absence of clinically significant bleeding.  If there is active bleeding, a higher threshold should be considered (100 × 109/L for intracranial bleeding, and 50 × 109/L for other sites of bleeding).  For neonates with known or suspected FNAIT, a paediatric haematologist should be consulted. | 4.1.5 |
| EOP15 | For neonates with known or suspected FNAIT, platelet count response to transfusion should be checked within 12 hours. | 4.1.5 |
| EOP16 | For infants with known or suspected FNAIT, random donor platelets should be used if antigen-matched platelets are not immediately available. Continued use of random donor platelets is acceptable if antigen-matched platelets cannot be obtained. Because of short survival of random donor platelets, repeated transfusion is likely to be needed. | 4.1.5 |
| EOP17 | For infants with FNAIT, IVIg may be considered.[20](#_ENREF_20) | 4.1.5 |

| **HLA-matched platelets** | | |
| --- | --- | --- |
| EOP18 | For platelet refractoriness attributable to non-immune causes such as splenomegaly or infection, fresh, ABO-compatible, single-donor apheresis platelets may improve platelet increment. | 4.1.6 |
| EOP19 | If the cause of platelet refractoriness is not obvious, investigation should include screening for HLA antibodies. HLA-matched platelets should be used if an HLA antibody is detected.  If the HLA antibody screen is negative or there is a poor response to HLA-matched platelets, screening for HPA antibodies should be undertaken, followed by use of HPA-matched platelets if positive. | 4.1.6 |
| EOP20 | In patients with inherited platelet disorders such as Bernard Soulier Syndrome and Glanzmann’s thrombasthenia, platelet transfusions should be avoided if possible, to reduce the patient’s risk of alloimmunisation. If platelet transfusion is unavoidable the patient should receive HLA-matched platelets. | 4.1.6 |
| **Intrauterine fetal blood component transfusion** | | |
| EOP21 | Management of pregnancies at risk of fetal anaemia or thrombocytopaenia should be undertaken in facilities with appropriate expertise in ultrasound imaging and invasive fetal interventions, and that have access to specific blood products and neonatal intensive care. | 4.2.1 |
| EOP22 | Pregnancies at risk of fetal anaemia should be assessed by Doppler ultrasound of the fetal MCA PSV, to determine whether FBS and IUT are necessary. | 4.2.1 |
| EOP23 | Pregnant women who have had a prior pregnancy with fetal or neonatal ICH or thrombocytopaenia due to FNAIT should be managed with IVIg.[20](#_ENREF_20) | 4.2.1 |
| EOP24 | FBS should be considered to assess response to IVIg in those who have had a previous child with ICH due to FNAIT. | 4.2.1 |
| **Minimisation of blood loss** | | |
| EOP25 | Strategies to safely minimise phlebotomy losses should be used for all neonatal and paediatric patients. Such strategies may include (where safe and feasible):  use of ‘as-needed’ rather than routine sampling  meticulous avoidance of blood overdraw  return of void volumes to sampling lines  use of closed inline sampling devices  judicious use and ‘on-time’ removal of sampling lines  optimal sampling technique and sample handling to minimise rejection of samples by laboratory  laboratory equipment that uses the smallest possible sample volumes  use of non-invasive techniques and POC devices  audit compliance and cumulative phlebotomy losses in selected groups of patients at regular intervals. | 4.3.6 |
| EOP26 | PCCs may be considered in neonatal and paediatric patients undergoing urgent surgery who are receiving VKAs.[21](#_ENREF_21) | 4.4.1 |
| EOP27 | PCCs may be considered to treat bleeding in paediatric patients at high risk of volume overload (e.g. those who have undergone cardiac surgery on CPB). | 4.4.1 |
| EOP28 | THAs may be considered in neonatal and paediatric surgical patients as an adjuvant to control bleeding. | 4.4.2 |
| EOP29 | The use of THAs should adhere to the manufacturer’s instructions and safety information. | 4.4.2 |
| **Critical bleeding** | | |
| EOP33 | Institutions that provide care for neonates and paediatric patients should have a critical bleeding protocol specific to such patients. | 4.6 |
| EOP34 | The critical bleeding protocol should outline the essential steps (including coordination and communication) to rapidly and effectively manage a patient who is at risk of or undergoing critical bleeding. | 4.6 |
| EOP35 | The critical bleeding protocol should include weight adjustments to guide blood product supply and administration. The clinician, in consultation with the haematologist or transfusion specialist, should tailor the type, volume and order of products given to the clinical circumstances. | 4.6 |
| AHCDO, Australian Haemophilia Centre Directors' Organisation; AI, adequate intake; ANH, acute normovolaemic haemodilution; CKD, chronic kidney disease; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; CRG, Clinical/Consumer Reference Group; EACA, epsilon amino-caproic acid; EOP, expert opinion point; ESA, erythropoiesis stimulating agent; FBS, fetal blood sampling; FFP, fresh frozen plasma; FNAIT, fetal and neonatal alloimmune thrombocytopaenia; Hb, haemoglobin; Hct, haematocrit; HDFN, haemolytic disease of the fetus and newborn; HLA, human leucocyte antigen; HPA, human platelet antigen; ICH, intracranial haemorrhage; IDA, iron deficiency anaemia; INR, international normalised ratio; IT, information technology; IUT, intrauterine transfusion; IV, intravenous; IVH, intraventricular haemorrhage; IVIg, intravenous immunoglobulin; K, Kell; KDIGO, Kidney Disease Improving Global Outcomes; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PCC, prothrombin complex concentrate; POC, point-of-care; PP, practice point; PSV, peak systolic velocity; R, recommendation; RBC, red blood cell; RDI, recommended daily intake; rFVIIa, recombinant activated factor VII; RNI, recommended nutrient intake; SCD, sickle cell disease; SCID, severe combined immunodeficiency; TAGVHD, transfusion-associated graft-versus-host disease; TCD, transcranial Doppler; THA, topical haemostatic agent; TXA, tranexamic acid; VKA, vitamin K antagonist | | |

# 1 Introduction

Patient blood management (PBM) aims to improve 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.

If blood components are likely to be indicated, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks (Appendix C). In the process of obtaining informed consent, wherever possible a clinician should allow the patient or parent sufficient time to ask questions, and should answer those questions.

This document, *Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics*, is the sixth in a series of six modules that focus on evidence-based PBM. The other five modules are listed in Table 1.1, below. Together, Module 2 (*Perioperative*)[*2*](#_ENREF_2)and Module 3 (*Medical*)[3](#_ENREF_3)cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*[6](#_ENREF_6) (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT).

## Development of the guidelines

### 1.1.1 Clinical need for these guidelines

Revision of the 2001 guidelines[6](#_ENREF_6) was needed because of:

increasing evidence of transfusion-related adverse outcomes, leading to the emergence of new practices, including restrictive transfusion strategies and the increased use of alternatives to transfusion in the management of anaemia

variable (and frequently poor) compliance with the recommendations of the 2001 guidelines, indicated by a high degree of variation in transfusion practices

failure of the 2001 guidelines to address a range of clinical settings where blood management is commonly required, including critical bleeding and massive transfusion, chronic medical conditions, obstetrics and paediatrics.

In response to the situation outlined above, the NHMRC, the Australian & New Zealand Society of Blood Transfusion (ANZSBT) and the National Blood Authority (NBA)[[1]](#footnote-1) agreed to develop a series of six patient-focused, evidence-based modules that together will comprise new PBM guidelines.

The six modules of the guidelines are being developed in three phases, as shown in Table 1.1.

Table 1.1 Phases of development of guideline modules

|  |  |
| --- | --- |
| Phase | Modules |
| I | 1 – Critical bleeding/massive transfusion[1](#_ENREF_1) |
|  | 2 – Perioperative[2](#_ENREF_2) |
| II | 3 – Medical[3](#_ENREF_3) |
|  | 4 – Critical care[4](#_ENREF_4) |
| III | 5 – Obstetrics and maternity[5](#_ENREF_5) |
|  | 6 – Neonatal and paediatrics |

## 1.2 Structure of the document and related materials

### 1.2.1 The document

This module includes:

*recommendations* – based on evidence from the systematic review

*practice points* – based on consensus decision making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but where clinicians require guidance to ensure good clinical practice

*expert opinion points* – based on consensus decision making, where relevant guidance that is outside of the scope of the systematic review is required.

The recommendations, practice points and expert opinion points are summarised in the plain English summary.

**RECOMMENDATION**

**BASED ON EVIDENCE**

**FROM THE**

**SYSTEMATIC REVIEW**

**EXPERT OPINION POINT**

YES

**PRACTICE POINT**

**BASED ON CONSENSUS OF THE CRG**

**SUFFICIENT HIGH- QUALITY DATA**

*YES*

*NO*

*YES*

*NO*

*NO*

**NO STATEMENT MADE**

The remainder of this document includes:

an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)

clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG, and recommendations and practice points, as appropriate (Chapter 3)

background questions (Chapter 4)

recommendations for future directions (Chapter 5)

information on implementing, evaluating and maintaining the guidelines (Chapter 6).

The document also includes appendixes that provide information on membership of the governance bodies for guideline development and transfusion risks; an overview of the blood sectors in Australia and New Zealand; a process report; information on blood component products; and guidance on dosing, assessment and optimisation of various products and situations in the neonatal and paediatric population. Finally, the document contains a list of references.

### 1.2.2 Related materials

Materials relevant to clinicians will be developed to accompany this module; these materials will be available online and in print from the NBA.

The technical report that underpins this document is also available online, in two volumes:

*Volume 1*[7](#_ENREF_7)  
This volume contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline.

*Volume 2*[8](#_ENREF_8)This volume contains appendixes that document the literature searches, study-quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.

# 2 Methods

The development of evidence-based clinical practice guidelines that meet NHMRC standards involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence.[22](#_ENREF_22) The methods used in applying this process to the development of this module are outlined below, and are given in full in the accompanying technical report. A summary of the overall process for development of this module is given in Appendix B.

## 2.1 Clinical research questions

### 2.1.1 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 CRG (Appendix A). The process is described in greater detail in the technical reports.[7-8](#_ENREF_7) The clinical research questions for systematic review (Box 2.1) 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 websites (e.g., NICE and CADTH), clinical trial registries and PreMedline.

Box 2.1 Systematic review questions

Questions 1–3 are relevant to all six modules of these guidelines; question 4 is specific to transfusion in a neonatal and paediatric setting (i.e. to this module).

* *Question 1* – In neonates/paediatric patients, what is the effect of RBC (allogeneic) transfusion on patient outcomes? (Interventional question)
* *Question 2* – In neonates/paediatric patients, what is the effect of non-transfusion interventions to increase the Hb concentration on morbidity, mortality, and need for RBC transfusion? (Interventional question)
* *Question 3* – In neonates/paediatric patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
* *Question 4* – In neonates/paediatric patients, what is the effect of strategies that minimise blood loss and/or reduce the need for RBC transfusion? (Interventional question)

FFP, fresh frozen plasma; Hb, haemoglobin; RBC, red blood cell

### 2.1.2 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.

Box 2.2 Background research questions

* *Background question 1* – For fetal, neonatal or paediatric patients, does selection of specific blood products, when compared with routine blood products improve outcomes?
* *Background question 2* – In fetuses at risk for thrombocytopaenia or anaemia, do particular strategies for detection, intrauterine transfusion and other management improve outcomes and/or reduce the need for neonatal transfusion?
* *Background question 3* – In neonatal and paediatric patients, do non-pharmacologic blood conservation strategies aimed at minimisation of blood loss from sampling reduce the incidence of red cell transfusion?
* *Background question 4* – In perioperative neonatal and paediatric patients undergoing cardiac surgery, do strategies to minimise blood loss reduce the need for transfusion?
* *Background question 5* – In neonates and children, what recommendations should be made for the detection, diagnosis and management of iron deficiency anaemia?
* *Background question 6* – In neonates and children, what recommendations should be made for dealing with critical bleeding?

## 2.2 Review and research

### 2.2.1 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.

To answer these questions, comprehensive search strategies were designed, as detailed in Volume 2 of the technical report.[8](#_ENREF_8) 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 (Chapter 3).

### 2.2.2 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.[8](#_ENREF_8) 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*.[23](#_ENREF_23)

### 2.2.3 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 Volume 1 of the technical report.[7](#_ENREF_7)

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

## 2.3 Development of evidence statements, recommendations and practice points

For each research question addressed by the systematic review, the body of evidence was consolidated into evidence statements and rated according to the matrix shown in Table 2.1, which considers five domains: evidence base, consistency, clinical impact, generalisability and applicability. For included studies, evidence base and consistency were derived directly from the literature identified for each research question, whereas clinical impact, generalisability and applicability were assessed with guidance from the CRG. To ensure that the best available evidence was used, studies of higher levels of evidence (i.e. Levels I or II) were included in preference to those presenting lower levels (i.e. Levels III or IV) of evidence. This minimised 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.

Evidence statements were only transformed into ‘action-oriented’ recommendations where:

the body of evidence was sufficient – that is, wherever the evidence yielded support for recommendations of at least NHMRC Grade C (see Table 2.2)

the question type was interventional – that is, it evaluated the effectiveness of an intervention.

The recommendations were carefully worded to reflect the strength of the body of evidence.

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation, the CRG developed practice points through a consensus-based process, to guide clinical practice. For all recommendations, practice points and expert opinion points, consensus was achieved; there were no dissenting views.

Table 2.1 Body of evidence matrix

| Component | A (✓✓✓) | B (✓✓) | C (✓) | D (X) | NA |
| --- | --- | --- | --- | --- | --- |
|  | Excellent | Good | Satisfactory | Poor | Not applicable |
| 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–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 | One study only |
| Clinical impact | Very large | Substantial | Moderate | Slight or restricted |  |
| Generalisability | Population/s studied in the body of evidence are the same as the target population for the guideline | Population/s studied in the body of evidence are similar to the target population for the guideline | 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 guideline | 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 guideline |  |
| Applicability | Directly applicable to the Australian health-care context | Applicable to the Australian health-care context, with a few caveats | Probably applicable to the Australian health-care context, with some caveats | Not applicable to the Australian health-care context |  |

Source: NHMRC 2009[24](#_ENREF_24)

Table 2.2 Definitions of NHMRC grades for recommendations

|  |  |
| --- | --- |
| Grade | Definition |
| A | Body of evidence can be trusted to guide practice |
| B | Body of evidence can be trusted to guide practice in most situations |
| C | Body of evidence provides some support for recommendation(s) but care should be taken in its application |
| D | Body of evidence is weak and recommendations must be applied with caution |

Source: NHMRC 2009[24](#_ENREF_24)

# 3 Clinical guidance

## 3.1 Introduction

### 3.1.1 Purpose and audience

This document is intended to assist and guide health-care professionals in making clinical decisions about blood management in neonatal and paediatric patients. Specific guidelines are needed for these age groups because there are considerable physiological differences between neonates and children at different developmental stages, and between children and adults. Transfusions can be lifesaving and improve health, but can also have adverse consequences. Both the benefits and adverse consequences of transfusions in neonatal and paediatric patients may be lifelong.

This chapter also outlines the need for guidance on:

red blood cell (RBC) transfusions in preterm infants (Appendix F)

paediatric haemoglobin (Hb) assessment and optimisation (Appendix G)

tranexamic acid (TXA) dosing (Appendix H)

intravenous iron (Appendix I)

calculation of transfusion volume (Appendix J)

critical bleeding protocol (Appendix K).

The resources in Appendixes F–K can be adapted to suit the local patient population and health-care setting.

### 3.1.2 Scope

This chapter provides clinical guidance in the form of recommendations (based on evidence) and practice points (based on CRG consensus). The guidance is organised around the four questions that formed that basis of the systematic review. Full details of the findings of the systematic review are given in the accompanying technical reports.[7-8](#_ENREF_7)

A diagnostic approach to anaemia in neonatal and paediatric patients is outside the scope of these guidelines. Factor replacement specific to patients with haemophilia is covered in other guidelines.[25](#_ENREF_25) Fetal transfusion is discussed in Chapter 4.

Relevant questions in Modules 1–4 have been considered specifically for neonatal and paediatric populations, including the following subgroups: medical, surgical and critical illness.

### 3.1.3 Patient population and setting

#### Patient population

##### Definitions

For the 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).

##### Aboriginal and Torres Strait Islander populations

The research protocol required the systematic reviewers to isolate included papers that addressed Aboriginal or Torres Strait Islander subgroups. No randomised controlled trials (RCTs) have been published that addressed the research questions in this population. Observational studies indicate that the rate of anaemia is high.[26-30](#_ENREF_26) Research is urgently required to inform targeted care. Specific issues relating to the care of Aboriginal or Torres Strait Islander children are addressed in Section 3.6, with expert opinion points provided.

#### Settings

The guidance given here applies to all settings where neonatal and paediatric patients are managed, including metropolitan, rural or remote areas. Where access to a haematologist or transfusion medicine specialist is limited, early consultation or referral is warranted.

### 3.1.4 Formation of evidence statements

The evidence statements given here and in Volume 1 of the technical report[7](#_ENREF_7) were created using a standard sentence structure, as shown in Table 3.1. This sentence structure was used where possible. However, in some cases, the order of the components was changed for clarity and to maintain correct grammar.

Table 3.1 Structure of evidence statements

|  |  |
| --- | --- |
| Content | Example |
| 1. A definition of the relevant population. | In very low birth weight infants (*<*1500 g) … |
| 2. A description of the intervention. | In very low birth weight infants (*<*1500 g), liberal RBC transfusion … |
| 3. A description of the effect on the outcome of interest. | In very low birth weight infants (*<*1500 g), liberal RBC transfusion may reduce cognitive delays … |
| 4. Where appropriate, a description of the comparator. | In very low birth weight infants (*<*1500 g), liberal RBC transfusion may reduce cognitive delays compared with restrictive RBC transfusion. |

The description of the effect of the intervention was also standardised, as shown in Table 3.2.

Table 3.2 Description of interventions

| Evidence | Structure of statement | Example |
| --- | --- | --- |
| Sufficiently powered, consistent evidence of an effect or no effect. | States strongly that there **is** an effect or no effect. | In very low birth weight infants (*<*1500 g), liberal RBC transfusion reduces (or ‘does not reduce’) cognitive delays compared with restrictive RBC transfusion. |
| Evidence of an effect, but a slight concern about underpowering or consistency. | States that there **may be** an effect. | In very low birth weight infants (*<*1500 g), liberal RBC transfusion may reduce cognitive delays compared with restrictive RBC transfusion. |
| Little evidence available, or evidence is conflicting or clearly underpowered. | States that the effect is **uncertain**. | In very low birth weight infants (*<*1500 g), the effect of liberal RBC transfusion compared with restrictive RBC transfusion on cognitive delays is uncertain. |
| No evidence available for a particular question or outcome. | States that the effect is **unknown**. | In infants, children and adolescents, the effect of RBC transfusion compared with no transfusion on mortality is unknown. |

## 3.2 Effect of RBC transfusion on outcomes

Question 1 (Interventional)

In neonates/paediatric patients, what is the effect of RBC (allogeneic) transfusion on patient outcomes?

RBC, red blood cell

Neonatal and paediatric patients are transfused to reduce morbidity and mortality, and improve quality of life. The literature search for this question aimed to establish whether receiving a RBC transfusion affects patient outcomes. The review examined the effect of RBC transfusions in neonates (both term and preterm), infants, children and adolescents. It considered studies that compared RBC transfusion with no transfusion or with a different RBC dose, and that compared liberal and restrictive transfusion strategies.

### 3.2.1 Neonatal patients – effect of RBC transfusion on patient outcomes

| Evidence statements – preterm and low birth weight infants (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.1 | In very low birth weight infants (*<*1500 g), the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.A in Volume 2 of the technical report.) | √ | NA | √ | √√√ | √ |
| ES1.2 | In preterm infants, the effect of RBC transfusion compared with no transfusion on a composite of mortality and severe morbidity is unknown. | NA | NA | NA | NA | NA |
| ES1.3 | In preterm infants, the effect of RBC transfusion compared with no transfusion on NEC is uncertain.  (See evidence matrix D1.B in Volume 2 of the technical report.) | √ | X | X | √√ | √ |
| ES1.4 | In preterm infants, the effect of RBC transfusion compared with no transfusion on ROP is uncertain.  (See evidence matrix D1.C in Volume 2 of the technical report.) | X | √ | X | √√ | √ |
| ES1.5 | In very low birth weight infants (*<*1500 g), the effect of RBC transfusion compared with no transfusion on IVH is uncertain.  (See evidence matrix D1.D in Volume 2 of the technical report.) | √ | NA | √ | √√√ | √ |
| ES1.6 | In very low birth weight infants (*<*1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is uncertain.  (See evidence matrix D1.E in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √√ |
| ES1.7 | In very low birth weight infants (*<*1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on a composite outcome of mortality and severe morbidity is uncertain.  (See evidence matrix D1.F in Volume 2 of the technical report.) | √√ | √√ | X | √√ | √ |
| ES1.8 | In very low birth weight infants (*<*1500 g), there is no difference between restrictive RBC transfusion or liberal RBC transfusion on the incidence of NEC, ROP or BPD.  (See evidence matrix D1.G in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √√ |
| ES1.9 | In very low birth weight infants (*<*1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on brain injury is uncertain.  (See evidence matrix D1.H in Volume 2 of the technical report.) | √√ | √√ | NA | √√ | √√ |
| ES1.10 | In very low birth weight infants (*<*1500 g), liberal RBC transfusion may reduce cognitive delays compared with restrictive RBC transfusion.  (See evidence matrix D1.I in Volume 2 of the technical report.) | √√ | NA | √ | √√ | √√ |
| ES1.11 | In very low birth weight infants (*<*1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on neurosensory impairment, cerebral palsy, and visual and hearing impairments is uncertain.  (See evidence matrix D1.I in Volume 2 of the technical report.) | √√ | NA | √ | √√ | √√ |
| BPD, bronchopulmonary dysplasia; ES, evidence statement; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; RBC, red blood cell; ROP, retinopathy of prematurity  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – preterm and low birth weight infants (RBC transfusion) | |
| R1 (Grade C) | In paediatric patients, including those who are critically ill, a restrictive transfusion strategy should be employed.a Higher Hb thresholds are appropriate in very low birth weight neonates.b  a See PP6 for guidance on a restrictive transfusion strategy. b See PP2 and PP3 for guidance for preterm neonates. |
| Practice points – preterm and low birth weight infants (RBC transfusion) | |
| PP1 | In neonatal and paediatric patients, the decision to give a RBC transfusion should not be dictated by a Hb concentration alone.a 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.  a See PP1 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP2 | Neonatal units should use a procedural guidelinea for RBC transfusion in preterm infants that includes the following:  age of infant  Hb or Hct  level of respiratory support  ongoing or anticipated red cell loss  nutritional status.  a See Appendix F (*RBC transfusions in preterm infants*). |
| PP3 | In preterm infants requiring transfusion, there is insufficient evidence to support or refute the use of either a restrictive or liberal RBC transfusion strategy. |
| PP4 | In neonatal patients, calculate transfusion volume (mL) based on weight and desired Hb increment.a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). |
| Hb, haemoglobin; Hct, haematocrit; PP, practice point; R, recommendation; RBC, red blood cell | |

#### Background

Most transfusions in neonates and infants born preterm are small-volume transfusions (10–20 mL/kg) given to treat anaemia of prematurity, with the aim of improving tissue oxygenation. However, the effects of this intervention on patient outcomes remain uncertain. There is considerable variability in practice in relation to Hb thresholds and other indications for RBC transfusion.

Neonates may also receive large-volume transfusion; for example, exchange transfusion to prevent kernicterus, or pump priming for cardiac surgery and extracorporeal membrane oxygenation (ECMO).

#### RBC transfusion versus no transfusion (or different RBC dose) in neonates

This review did not identify any Level I or II studies that compared RBC transfusion with no transfusion or different RBC doses in neonates and infants born preterm. Therefore, the evidence base comprised two systematic reviews of Level III studies (one of poor quality[31](#_ENREF_31) and one of good quality[32](#_ENREF_32)) and 14 Level III-2 studies.[33-46](#_ENREF_33)

##### Mortality

One retrospective cohort study investigated factors associated with survival among 194 preterm infants with very low birth weight admitted to the neonatal intensive care unit (NICU).[43](#_ENREF_43) It reported no significant difference among those who received a transfusion (63.1%) compared with those not transfused (65.5%).

One retrospective cohort study of fair quality assessed the association between RBC transfusion and mortality among 1077 preterm infants with very low birth weight (defined as birth weight <1250 g).[36](#_ENREF_36) After controlling for variables independently associated with higher neonatal morbidity, the authors concluded that:

* the relative risk of in-hospital mortality remained significantly increased among infants who received at least one RBC transfusion before day 28 of life
* the relative risk of death beyond the neonatal period remained significant among infants who received more than two RBC transfusions during their hospital stay, compared with infants who received one or two RBC transfusions.

##### Composite of mortality and severe morbidity

No studies compared RBC transfusion with no transfusion in preterm infants, and reported on a composite of mortality and severe morbidity such as bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP) or brain injury on ultrasound.

##### Severe morbidity

BPD

No studies compared RBC transfusion with no transfusion in preterm infants, and reported on the outcome of BPD.

NEC

Two systematic reviews of Level III studies[31-32](#_ENREF_31) and four additional Level III-2 cohort and case–control studies[35](#_ENREF_35); [37](#_ENREF_37); [44-45](#_ENREF_44) examined the association between RBC transfusion and NEC in preterm infants. Both of the systematic reviews reported a significant association between RBC transfusion and NEC; however, the Level III studies reported conflicting results. The relationship between RBC transfusion and NEC is unclear because:

* the relationship between the timing of administration of transfusion and development of NEC varied between studies; in some studies, onset of NEC may have occurred before transfusion, and in others, some cases of NEC occurred so long after transfusion that the relationship between the two was unclear
* in some studies, there was a high risk of bias because of incomplete reporting of outcome data
* observational studies cannot rule out the possibility of common risk factors for transfusion and development of NEC that could result in association without causation.

ROP

Six Level III studies of poor to fair quality examined the association between RBC transfusion and ROP in preterm infants.[38-42](#_ENREF_38); [46](#_ENREF_46) After adjusting for potential confounders, three studies[40-41](#_ENREF_40); [46](#_ENREF_46) reported a significant association between RBC transfusion and ROP, but the other three studies[38-39](#_ENREF_38); [42](#_ENREF_42) found that the association between RBC transfusion and the incidence of ROP was no longer significant.

Brain injury on ultrasound

One Level III study examined the association between RBC transfusion and severe intraventricular haemorrhage (IVH) in preterm infants.[34](#_ENREF_34) The study assessed various risk factors associated with the development of severe IVH, and reported a significant association between RBC transfusion and the development of severe IVH by 1 month. However, this association is uncertain because it is based on a single retrospective case–control study that has not been reproduced.

Neurodevelopmental disability

No studies compared RBC transfusion to no transfusion in preterm infants, and reported on neurodevelopmental disability.

Transfusion-related serious adverse events

No studies compared RBC transfusion with no transfusion in preterm infants, and reported on transfusion-related serious adverse events such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), haemolytic transfusion reactions, transfusion-transmitted infections, transfusion-associated graft-versus-host disease (TAGVHD) and anaphylactic reactions.

#### Restrictive RBC transfusion versus liberal RBC transfusion in neonates

Four good-quality Level I studies compared a restrictive RBC transfusion protocol with a liberal protocol in preterm or very low birth weight infants.[47-50](#_ENREF_47) All four systematic reviews included data from three RCTs,[51-53](#_ENREF_51) involving a total of 590 very low birth weight infants. No additional Level II studies were identified that reported outcomes relevant to the research question.

##### Mortality

All studies reported no significant difference between a restrictive and a liberal RBC transfusion strategy on the outcome of mortality.

##### Composite of mortality and severe morbidity

The review by Whyte (2011)[50](#_ENREF_50) assessed the effect of different transfusion strategies on a composite of mortality and severe morbidity before first hospital discharge. It reported no significant difference in death or severe morbidity. Whyte (2011)[50](#_ENREF_50) also reported data on a composite of mortality and severe brain injury before first hospital discharge, and again found no statistically significant difference between restrictive and liberal transfusion strategies.

In a predefined follow-up to the PINT 2006[53](#_ENREF_53) study, Whyte (2011)[50](#_ENREF_50) assessed a composite of mortality and cognitive delay, defined as a mental development index (MDI) <70 (>2 standard deviations below age norm) at 18–21 months post-transfusion. No significant difference was found between infants randomised to a restrictive or a liberal RBC transfusion strategy at birth, although the point estimate leaned in favour of liberal transfusion. A post-hoc analysis that assessed a composite of mortality and cognitive delay demonstrated statistical significance.

##### Severe morbidity

Five Level II studies compared restrictive and liberal transfusion strategies among preterm infants, and reported severe morbidity outcomes including ROP, BPD and NEC.[51-55](#_ENREF_51) None of the studies reported significant differences in these outcomes.

Brain injury on ultrasound

Two systematic reviews did not demonstrate any significant difference in brain injury between transfusion strategies.[48](#_ENREF_48); [50](#_ENREF_50)

Neurodevelopmental disability

One fair-quality Level II study (Whyte 2009)[56](#_ENREF_56) compared restrictive and liberal transfusion strategies in relation to neurodevelopmental disability in preterm infants. This study followed up the infants enrolled in the PINT 2006[53](#_ENREF_53) study at 18–21 months post-transfusion. It found no significant difference between restrictive and liberal RBC transfusion strategies for cerebral palsy, severe visual and hearing impairment, or any neurosensory impairment.

Transfusion-related serious adverse events

One Level II study with insufficient power to detect a difference in transfusion-related serious adverse events reported no cases of TACO, TRALI, haemolytic transfusion reactions, transfusion-transmitted infections, TAGVHD or anaphylactic reactions.[51](#_ENREF_51)

Clinical commentary – effect of RBC transfusion on patient outcomes in neonates

In preterm infants, the physiological decline in circulating RBCs is more pronounced than in term infants. Factors contributing to anaemia of prematurity include rapid growth, inadequate erythropoiesis and the phlebotomy blood losses that may occur within the first few weeks of life. The anaemia can be treated with RBC transfusions, which raise Hb levels and help to increase red cell mass. However, concerns have been raised about the use of RBC transfusions in preterm infants, because of a potential association with various adverse events (e.g. ROP, BPD, NEC and IVH) to which preterm infants are particularly vulnerable. Further, the use and dosing of transfusion varies widely, because neither the appropriate Hb thresholds nor, the other triggers for RBC transfusion have a strong evidence basis.

The current systematic review suggests that transfusion in preterm infants is associated with increased in-hospital mortality. However, the increase in relative risk is modest and could be attributable to unmeasured confounding variables. There is no evidence to support an association between RBC transfusion and BPD, ROP or neurodevelopmental disability. A number of studies have reported a relationship between RBC transfusion and NEC in preterm neonates. In contrast, RCTs comparing restrictive versus liberal transfusion strategies in this population suggest that a more liberal transfusion strategy does not increase the risk of NEC. Therefore, although observational studies of preterm patients suggest an association between RBC transfusion and NEC, causation has not been established.

Overall, it is unclear whether the general use of RBC transfusion should be guided by a restrictive or a liberal transfusion strategy. Recent evidence highlights the contribution to improved clinical outcomes of higher oxygen saturation targets in the neonatal period.[57](#_ENREF_57) However, the oxygen saturation targets used in the studies comparing restrictive and liberal strategies were not clearly specified. Hence, in the setting of contemporary oxygen saturation targets of 91–95%, the effect of a restrictive versus liberal transfusion strategy on patient outcomes remains unknown.

In the current systematic review, no significant difference between restrictive and liberal RBC transfusion strategies was observed for neonatal mortality. However, post-hoc analysis of the PINT 2006 study[53](#_ENREF_53) suggested that a liberal transfusion threshold led to reductions in both cognitive delay and the composite of mortality and cognitive delay. Further evidence will become available from two large RCTs currently underway. These RCTs, which are using the higher oxygen saturation target band, aim to determine the effect of restrictive versus liberal transfusion thresholds on neonatal morbidity, mortality and developmental outcomes.

### 3.2.2 Infants, children and adolescents – effect of RBC transfusion on patient outcomes

| Evidence statements – infants, children and adolescents (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.12 | In infants, children and adolescents, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES1.13 | In infants, children and adolescents, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – infants, children and adolescents (RBC transfusion) | |
| R1 (Grade C) | In paediatric patients, including those who are critically ill, a restrictive transfusion strategy should be employed.a Higher Hb thresholds are appropriate in very low birth weight neonates.b  a See PP6 for guidance on a restrictive transfusion strategy. b See PP2 for guidance for very low birth weight neonates. |
| Practice points – infants, children and adolescents (RBC transfusion) | |
| PP5 | For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:  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. |
| PP6 | In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensusa 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.  a See PP3 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment. a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). |
| PP9 | 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.a  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| PP10 | 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. |
| PP12 | In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.a A template protocol is provided within the module.b  a The use of the word ‘protocol’ is not strictly prescriptive. b The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. |
| CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell | |

#### Background

Paediatric patients – including infants, children and adolescents – do not often receive RBC transfusions. The paediatric groups that most commonly receive RBC transfusions are:

* haemato-oncology patients receiving myelosuppressive chemotherapy
* paediatric intensive care unit (PICU) patients, particularly those undergoing cardiac surgery
* patients with congenital anaemia or haemoglobinopathies receiving chronic transfusions.

The systematic review identified no studies that compared the safety and effectiveness of RBC transfusions with transfusion (or with different dose) in infants, children or adolescents.

#### Restrictive RBC transfusion versus liberal RBC transfusion in infants, children and adolescents

The systematic review identified no studies that compared safety and efficacy of restrictive and liberal transfusion strategies in paediatric medical patients.

One Level I study[58](#_ENREF_58) examined the effect of transfusion thresholds on clinical outcomes in surgical and medical patients of any age (excluding neonates). The review identified 19 RCTs, one of which[59](#_ENREF_59) was in a critical-care paediatric population and is considered below (see Section 3.2.7).

The findings of the Carson (2012)[58](#_ENREF_58) review were largely based on adult surgical patients; hence, their generalisability to the paediatric medical population is limited. That review indicated that a restrictive transfusion strategy reduced both the risk of receiving a RBC transfusion and the volume of RBCs transfused. However, the included studies varied in their definition of a restrictive and liberal transfusion policy. No difference between the strategies was detected in relation to rate of adverse events (i.e. mortality, pneumonia and thromboembolism); however, in-hospital mortality was lower with a restrictive than with a liberal transfusion policy.

Clinical commentary – effect of RBC transfusion on patient outcomes in infants, children and adolescents

In the absence of direct evidence to support recommendations for the medical paediatric population, evidence from other patient groups, expert CRG consensus and other modules in this series (*Medical*,[3](#_ENREF_3) *Perioperative*[2](#_ENREF_2) and *Critical Care*[4](#_ENREF_4)) was applied to derive a series of practice points.

### 3.2.3 Medical: neonatal and paediatric patients with SCD – effect of RBC transfusion on patient outcomes

| Evidence statements – SCD (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.14 | In neonates and infants with SCD, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES1.15 | In children and adolescents with SCD, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.J in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √√ |
| ES1.16 | In neonates and infants with SCD, the effect of RBC transfusion compared with no transfusion on stroke occurrence is unknown. | NA | NA | NA | NA | NA |
| ES1.17 | In children and adolescents with sickle cell anaemia or sickle beta thalassemia who have been assessed to be at increased risk of stroke,a ongoing prophylactic RBC transfusion compared with no RBC transfusion (or cessation of RBC transfusions) reduces stroke occurrence.  (See evidence matrix D1.K in Volume 2 of the technical report.) | √√ | √√√ | √√√ | √√√ | √√ |
| ES1.18 | In neonatal and paediatric patients with SCD, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES1.19 | In neonatal and paediatric patients with SCD, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on stroke is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; RBC, red blood cell; SCD, sickle cell disease  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – SCD (RBC transfusion) | |
| R2 (Grade A) | In children and adolescents with SCD who have been assessed to be at increased risk of stroke,a ongoing prophylactic RBC transfusions are recommended because they reduce stroke occurrence.b  a Assessed by TCD ultrasonography[9](#_ENREF_9) and MRI.[10](#_ENREF_10) b See PP11 for methods of assessment. |
| Practice points – SCD (RBC transfusion) | |
| PP7 | 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.a  a See PP23 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP11 | Children and adolescents with SCD should be assessed for stroke risk using both TCD ultrasonography[9](#_ENREF_9) and MRI.[10](#_ENREF_10) |
| Hb, haemoglobin; MRI, magnetic resonance imaging; PP, practice point; R, recommendation; RBC, red blood cell; SCD, sickle cell disease; TCD, transcranial Doppler  Note: The Phase III TCD With Transfusions Changing to Hydroxyurea (TWiTCH) trial[60](#_ENREF_60) comparing RBC transfusion to hydroxyurea in paediatric sickle cell patients was stopped early, because hydroxyurea was found to be as effective as transfusions in lowering the mean TCD velocity of blood flow. Complete data, including the secondary outcome of primary stroke, are not yet available. We await publication of the full trial results before changes to the current recommendations (R1 and R4) and practice points (PP11) are made. | |

#### Background

Sickle cell disease (SCD) is caused by homozygous inheritance of the HbS allele or compound heterozygous inheritance of that allele with another abnormality of the beta globin gene, such as HbC or beta thalassaemia. Important clinical manifestations of SCD in paediatric patients include splenic sequestration, haemolysis, aplastic crises, priapism, infection, stroke and recurrent painful vaso-occlusive episodes such as dactylitis and acute chest syndrome. Most children with SCD in developed countries will survive to adulthood; however, life expectancy may be reduced.

RBC transfusions are an important treatment strategy in the management of acute sickle complications and in the prevention of long-lasting complications such as stroke. During childhood, at least 20% of children with SCD will have silent ischaemic lesions that are visible on magnetic resonance imaging (MRI), and these lesions are associated with an increased incidence of clinical stroke.[61-62](#_ENREF_61)

Regular RBC transfusion usually leads to iron overload, which is typically treated with iron chelation. SCD patients are also at significant risk of haemolytic transfusion reactions and red cell alloimmunisation. High rates of alloimmunisation are seen in SCD patients receiving chronic transfusions, because of the high transfusion rates in these patients, and antigenic differences between donor and recipient populations.

#### RBC transfusion versus no transfusion (or different RBC dose) in paediatric patients with SCD

Two good-quality systematic reviews examined the effect of RBC transfusion in paediatric patients with SCD.[63-64](#_ENREF_63) These reviews included two good-quality Level II studies: the STOP trial,[9](#_ENREF_9) which randomised children (aged 2–16 years) at high risk of stroke based on transcranial Doppler (TCD) screening to either RBC transfusion or standard care (no transfusion); and the STOP 2 trial,[65](#_ENREF_65) which randomised children (aged 2–16 years) at high risk of stroke to continued RBC transfusions or cessation of transfusion therapy after 30 months of transfusions (halted transfusion group).

Two additional Level II studies of fair to poor quality were identified by the literature review.[10](#_ENREF_10); [66](#_ENREF_66) The SIT trial (Silent Cerebral Infarct Multi-centre Clinical Trial) compared the effect of RBC transfusions with no transfusion on cerebral infarction among paediatric patients (aged 5–15 years) with SCD and at least one infarct-like lesion detected by MRI.[10](#_ENREF_10) The second trial reported stroke incidence and silent infarct data from the STOP cohort at 36 months.[66](#_ENREF_66)

##### Mortality

Three Level II studies reported mortality and found no significant difference between treatment groups.[9-10](#_ENREF_9); [65](#_ENREF_65) However, the studies were underpowered for this outcome.

##### Stroke

Two systematic reviews[63-64](#_ENREF_63) and the two RCTs[10](#_ENREF_10); [66](#_ENREF_66) examined the effect of RBC transfusions on stroke incidence. A meta-analysis for stroke incidence was not performed because of differences in patient populations and study design.

The STOP trial demonstrated a significantly reduced risk of stroke in children with SCD and abnormal TCD velocities who commenced regular blood transfusions, compared with those who received no transfusion.[9](#_ENREF_9)

The STOP 2 trial was closed early owing to the concerns about the increased risk of stroke in the halted transfusion group.[65](#_ENREF_65) More strokes were reported in the halted transfusion group, although this did not reach statistical significance. However, in the halted transfusion group, the number of patients reverting to abnormal TCD velocities increased, implying increased stroke risk.

The 36-month follow-up study from the original STOP cohort found that long-term transfusion therapy continued to reduce the risk of stroke.[66](#_ENREF_66)

In children with SCD and known silent infarcts in the SIT trial, regular RBC transfusion compared with standard care (no transfusion) reduced the rate of neurological events, including cerebral infarction and transient ischaemic attacks.[10](#_ENREF_10)

##### Transfusion-related serious adverse events

One Level I study[63](#_ENREF_63) and the SIT trial[10](#_ENREF_10) reported the incidence of transfusion-related serious adverse events, including RBC alloimmunisation and transfusion reactions. As would be expected, transfusion-related adverse events, including alloimmunisation, and febrile and non-febrile transfusion reactions were much higher in the groups exposed to more transfusions.

##### Functional or performance measures

No studies reported functional or performance measures.

Clinical commentary – effect of RBC transfusion in paediatric patients with SCD

Children and adolescents with SCD at high risk of stroke should commence a long-term chronic transfusion program to reduce their risk of stroke occurrence (see R2). This recommendation accords with the recent National Institutes of Health (NIH) guidelines on management of SCD,[67](#_ENREF_67) which recommend that children with HbSS or HbS/B0 thalassaemia and elevated TCD should be referred for chronic transfusion therapy.

Paediatric patients with SCD should be assessed for their risk of stroke by TCD and MRI (see PP11). MRI is included because of the high number of children with evidence of silent cerebral ischaemia without clinical symptoms enrolled in the SIT trial. That trial screened 1074 eligible participants (aged 5–15 years) with MRI, and found that 379 children and adolescents (35%) had evidence of silent infarction without clinical symptoms. The current NIH guidelines do not recommend screening of patients with genotypes HbS/B+ thalassaemia or HbSC, or screening of asymptomatic children with MRI. However, the NIH guidelines were based on a literature review up to July 2014, which did not capture the SIT trial publication.[10](#_ENREF_10)

In view of increased RBC alloimmunisation in patients with SCD undergoing long-term transfusion, patients should have an extended RBC phenotype before their first transfusion. For specific guidance on transfusion support, refer to the ANZSBT *Guidelines for transfusion laboratory practice* *in the pretransfusion, antenatal and perinatal setting* [under development] and background question 1 (Section 4.1).

### 3.2.4 Medical: neonatal and paediatric patients with beta thalassaemia – effect of RBC transfusion on patient outcomes

#### Background

Beta thalassaemia major is an inherited disorder of reduced beta globin chain synthesis that causes severe anaemia. The aim of RBC transfusion in this condition is to treat severe anaemia, prevent early mortality, and promote growth, development, wellbeing and quality of life. It includes minimising or preventing bone marrow expansion that leads to bone deformities such as maxillary hyperplasia and extramedullary haematopoiesis causing hepatosplenomegaly.

#### RBC transfusion versus no transfusion (or different dose) in paediatric patients with beta thalassaemia

This systematic review did not identify any Level I or Level II studies in paediatric patients with beta thalassaemia. Module 3 (*Medical*[3](#_ENREF_3)) identified two prospective cohort studies[68-69](#_ENREF_68) and one retrospective cohort study[70](#_ENREF_70) that investigated the relationship between pretransfusion Hb concentration and transfusion volume in patients with beta thalassaemia. Masera et al (1982)[69](#_ENREF_69) found that patients with a mean pretransfusion Hb concentration of 102 g/L required significantly lower transfusion volumes than those with higher pretransfusion Hb levels.

Clinical commentary – effect of RBC transfusion in paediatric patients with beta thalassaemia

In patients with beta thalassaemia, the widely adopted pretransfusion Hb concentration of 90–100 g/L was developed empirically after trials of lower Hb levels were found to lead to complications (e.g. bone marrow expansion) from undertransfusion.

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. In those receiving a chronic transfusion program (e.g. beta thalassaemia or haemoglobin­opathies) transfusion volume (mL) should be based on weight and desired Hb increment (see Appendix J).

### 3.2.5 Medical: paediatric patients with cancer – effect of RBC transfusion on patient outcomes

| Evidence statements – anaemia associated with cancer (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.20 | In neonatal patients with anaemia associated with cancer, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES1.21 | In paediatric patients with anaemia associated with cancer, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.L in Volume 2 of the technical report.) | X | NA | NA | √√ | X |
| ES1.22 | In neonatal and paediatric patients with anaemia associated with cancer, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice points – anaemia associated with cancer (RBC transfusion) | |
| PP5 | For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:  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. |
| PP6 | In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensusa 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.  a See PP3 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment. a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). |
| PP9 | 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.a  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell | |

#### Background

Paediatric patients with cancer often develop anaemia as a result of bone marrow infiltration by malignancy, or treatments such as chemotherapy, radiation and haematopoietic stem cell transplantation. Anaemia can increase symptoms of fatigue, and may affect functional status and quality of life.

The most frequent treatment used to treat cancer-induced anaemia or chemotherapy-induced anaemia is RBC transfusion. This treatment can rapidly correct anaemia and the associated symptoms; however, the effect may be temporary, and all patients receiving regular transfusions are at risk of transfusion reactions, circulatory overload, infection and alloimmunisation.

#### RBC transfusion versus no transfusion (or different RBC dose) in paediatric patients with cancer

One poor-quality retrospective longitudinal study (Level III) compared the effect of cumulative transfusion of more than five units of RBC with transfusion of one to five units or no transfusion on overall survival in children (aged <15 years) with acute lymphoblastic leukaemia.[71](#_ENREF_71)

##### Mortality

The Level III study reported an increased risk of mortality in those transfused with more than five units of RBCs; however, the study was underpowered.

Clinical commentary – effect of RBC transfusion in paediatric patients with cancer

This literature review provided insufficient evidence to formulate recommendations. However, guidance relating to paediatric patients with cancer can be found in several practice points (see PP5, PP6, PP8 and PP9).

Paediatric patients with cancer are at risk of concurrent nutritional deficiencies such as iron deficiency, which may contribute to their anaemia. These deficiencies should be screened for and treated appropriately.

### 3.2.6 Neonatal and paediatric patients undergoing surgery – effect of RBC transfusion on patient outcomes

| Evidence statements – surgical (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.27 | In neonatal patients undergoing surgery, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES1.28 | In paediatric patients (<16 kg) undergoing cardiac surgery, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.N in Volume 2 of the technical report.) | √ | NA | NA | √√ | √ |
| ES1.29 | In paediatric patients who have received a liver transplant, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.O in Volume 2 of the technical report.) | √ | NA | NA | √√ | √ |
| ES1.30 | In neonatal and paediatric patients undergoing surgery, the effect of RBC transfusion compared with no transfusion on new or progressive MODS is unknown. | NA | NA | NA | NA | NA |
| ES1.31 | In neonatal and paediatric patients undergoing surgery, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is uncertain.  (See evidence matrix D1.P in Volume 2 of the technical report.) | √√ | √√√ | NA | √√√ | √√ |
| ES1.32 | In neonatal and paediatric patients undergoing surgery, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on new or progressive MODS is uncertain.  (See evidence matrix D1.Q in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES, evidence statement; MODS, multiple organ dysfunction syndrome; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – surgical (RBC transfusion) | |
| R1 (Grade C) | In paediatric patients, including those who are critically ill, a restrictive transfusion strategy should be employed.a Higher Hb thresholds are appropriate in very low birth weight neonates.b  a See PP6 for guidance on a restrictive transfusion strategy. b See PP2 and PP3 for guidance for preterm neonates. |
| Practice points – surgical (RBC transfusion) | |
| PP1 | In neonatal and paediatric patients, the decision to give a RBC transfusion should not be dictated by a Hb concentration alone.a 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.  a See PP1 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP3 | In preterm infants requiring transfusion, there is insufficient evidence to support or refute the use of either a restrictive or liberal RBC transfusion strategy. |
| PP5 | For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following:  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. |
| PP6 | In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensusa 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.  a See PP3 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment. a, b  a See Appendix F (*RBC transfusions in preterm infants*). b See Appendix J (*Transfusion volume calculation for neonates, infants and small children*). |
| PP9 | 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.a  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| PP12 | In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.a A template protocol is provided within the module.b  a The use of the word ‘protocol’ is not strictly prescriptive. b The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. |
| CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell | |

#### Background

Paediatric patients undergoing major surgery are at risk of blood loss. Hence, they may require perioperative RBC transfusion to improve tissue oxygenation, and to treat hypovolaemia and anaemia.

Neonates and paediatric patients undergoing cardiothoracic surgery for congenital cardiac disease are at significant risk of perioperative bleeding. These patients may be hypoxic and polycythaemic, and have altered coagulation profiles. Their surgeries are complex, often necessitating long cardiopulmonary bypass (CPB) times and extended periods of hypothermia.

CPB often requires large volumes of blood to prime the CPB circuit, to prevent dilutional anaemia at the start of the surgery. CPB causes platelet dysfunction, a dilutional coagulopathy and abnormal fibrinolysis. All of these factors contribute to the higher bleeding tendency and increased transfusion requirements seen in this patient population.

Other paediatric surgical procedures associated with significant blood loss that may necessitate RBC transfusion include liver transplantation, and surgery for scoliosis or craniosynostosis.

#### RBC transfusion versus no transfusion (or different RBC dose) in neonatal and paediatric patients undergoing surgery

The review identified three Level III-2 studies of fair to good quality that compared RBC transfusion with no transfusion (or alternate dose) in neonatal and paediatric patients undergoing surgery.[72-74](#_ENREF_72) Two studies were conducted in the neonatal and paediatric cardiac surgery setting[72](#_ENREF_72); [74](#_ENREF_74) and one in paediatric liver transplantation patients.[73](#_ENREF_73)

##### Mortality

Mortality rates were low in the three included studies, and the studies were underpowered for this outcome.[72-74](#_ENREF_72) Two studies reported mortality in cardiac surgery patients.[72](#_ENREF_72); [74](#_ENREF_74) Kneyber (2013)[72](#_ENREF_72) found that RBC transfusion had no effect on mortality, whereas Redlin (2013)[74](#_ENREF_74) reported higher mortality rates in those patients receiving intraoperative transfusion compared with those receiving postoperative or no transfusion. In paediatric patients undergoing liver transplantation surgery, mortality rates increased in proportion to the number of RBC units received both during and after surgery.[73](#_ENREF_73)

##### New or progressive multiple organ dysfunction syndrome

No evidence was identified related to multiple organ dysfunction syndrome (MODS).

#### Restrictive RBC transfusion versus liberal RBC transfusion in neonatal and paediatric patients undergoing surgery

One Level I study compared a restrictive and liberal RBC transfusion strategy in neonatal or paediatric patients undergoing cardiac surgery for congenital heart disease.[75](#_ENREF_75) The review identified two Level II studies[76-77](#_ENREF_76) of poor to good quality. It also identified one good-quality Level II trial[78](#_ENREF_78) that reviewed postoperative general surgery patients, and another trial[79](#_ENREF_79) that met the inclusion criteria of this systematic review, but was stopped early and did not provide usable data.

Two of the Level II studies[77-78](#_ENREF_77) reported data from two separate subgroups enrolled in the TRIPICU (Transfusion Requirements in Pediatric Intensive Care Units) study,[59](#_ENREF_59) which is reported in the critical care section (Section 3.2.7).

##### Mortality

Three Level II studies reported mortality and did not find a significant difference between transfusion strategies.[76-78](#_ENREF_76)

##### New or progressive MODS

Two Level II studies reported outcomes for MODS.[77-78](#_ENREF_77) Both found no significant difference in new or progressive MODS between transfusion strategies.

##### Transfusion-related serious adverse events

One Level II study reported transfusion-related serious adverse events.[77](#_ENREF_77) It found no significant difference in the number of transfusion reactions between transfusion groups, but was underpowered for this outcome.

Clinical commentary – effect of RBC transfusion in neonatal and paediatric patients undergoing surgery

In the absence of direct evidence to support recommendations for RBC transfusion in neonatal and paediatric patients undergoing surgery, evidence from other patient groups, expert CRG consensus and other modules in this series (*Medical*,[3](#_ENREF_3) *Perioperative*[2](#_ENREF_2) and *Critical care*[4](#_ENREF_4)) was applied to derive a series of practice points (see R1 and PPs 1, 3, 5, 6, 8, 9 and 12).

In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiency should be identified, evaluated and managed to minimise RBC transfusion.

RBC transfusions may be administered in the perioperative period to replace blood loss and treat anaemia. Neonates and paediatric patients have age-dependent normal reference ranges for Hb; however, the optimal Hb threshold for transfusion is unknown.

Any transfusion has potential risks such as transfusion reactions, circulatory overload, infection and alloimmunisation.

### 3.2.7 Critically ill neonatal and paediatric patients – effect of RBC transfusion on patient outcomes

| Evidence statements – critically ill (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES1.33 | In critically ill neonatal and paediatric patients, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.R in Volume 2 of the technical report.) | √ | √√ | X | √√ | √ |
| ES1.34 | In critically ill neonatal and paediatric patients, the effect of RBC transfusion compared with no transfusion on new or progressive MODS is unknown. | NA | NA | NA | NA | NA |
| ES1.35 | In critically ill neonatal and paediatric patients, restrictive RBC transfusion compared with liberal RBC transfusion does not appear to have an effect on new or progressive MODS.  (See evidence matrix D1.S in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES1.36 | In critically ill neonatal and paediatric patients, restrictive RBC transfusion compared with liberal RBC transfusion does not appear to have an effect on mortality.  (See evidence matrix D1.T in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES, evidence statement; MODS, multiple organ dysfunction syndrome; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – critically ill (RBC transfusion) | |
| R1 (Grade C) | In paediatric patients, including those who are critically ill, a restrictive transfusion strategy should be employed.a Higher Hb thresholds are appropriate in very low birth weight neonates.b  a See PP6 for guidance on a restrictive transfusion strategy. b See PP2 and PP3 for guidance for preterm neonates. |
| Practice point – critically ill (RBC transfusion) | |
| PP12 | In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.a A template protocol is provided within the module.b  a The use of the word ‘protocol’ is not strictly prescriptive.  b The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. |
| Hb, haemoglobin; PP, practice point; R, recommendation | |

#### Background

Neonatal and paediatric patients are at risk of anaemia in the critical care setting because of factors such as the underlying illness, small circulating blood volume, proportionally high phlebotomy losses, surgical or trauma-related blood loss and malnutrition. In infants, physiological anaemia may also contribute.

Critically ill neonates and children have high rates of RBC transfusion. Such transfusion may be lifesaving and should not be withheld in the actively bleeding or haemodynamically unstable patient. However, for patients with mild to moderate anaemia without haemodynamic compromise, the benefit of RBC transfusion is uncertain.

Any transfusion has potential risks such as transfusion reactions, circulatory overload, infection and alloimmunisation.

#### RBC transfusion versus no transfusion (or different RBC dose) in critically ill neonatal and paediatric patients

The review identified three retrospective cohort studies (Level III-2) of poor to fair quality that compared the effect of RBC transfusions with no transfusion in critically ill neonatal and paediatric patients.[80-82](#_ENREF_80) Of the three studies, one involved paediatric patients with traumatic brain injury,[80](#_ENREF_80) one infants and children with blunt abdominal trauma and liver laceration,[81](#_ENREF_81) and one paediatric trauma patients.[82](#_ENREF_82)

The three studies demonstrated an association between RBC transfusion and mortality.[80-82](#_ENREF_80) However, it was not possible to undertake a meta-analysis because of variable study characteristics, patient populations and the presence of confounders in the high mortality groups.

This literature review identified no studies that assessed the safety and efficacy of RBC transfusion compared with no RBC transfusion in relation to MODS in critically ill patients.

Only one study reported rates of transfusion-related serious adverse events; it reported nine febrile reactions among 81 transfused patients.[82](#_ENREF_82)

#### Restrictive RBC transfusion versus liberal RBC transfusion in critically ill neonatal and paediatric patients

Two good-quality systematic reviews compared the effect of a restrictive and a liberal RBC transfusion strategy in critically ill patients.[83-84](#_ENREF_83) Of these, one[83](#_ENREF_83) reviewed the transfusion threshold on clinical outcomes in surgical and medical patients of any age (excluding neonates); the other[84](#_ENREF_84) included neurocritically ill adult and paediatric patients admitted to intensive care unit (ICU). Both reviews included the paediatric RCT TRIPICU[59](#_ENREF_59) – a good-quality multicentre RCT of critically ill paediatric patients aged 3 days to 14 years who were randomised to a restrictive (70 g/L) or liberal (95 g/L) threshold for transfusion.

##### Mortality

The TRIPICU study reported 28-day mortality and in-PICU mortality.[59](#_ENREF_59) Desjardins et al (2012)[84](#_ENREF_84) reviewed a subgroup of the TRIPICU study. Both analyses found no difference in mortality rates when comparing restrictive and liberal transfusion strategies.

##### New or progressive MODS

New or progressive MODS was reported in the TRIPICU study;[59](#_ENREF_59) and Desjardins et al (2012)[84](#_ENREF_84)reported a subgroup of this study. Both analyses showed no significant differences for any MODS outcome when comparing restrictive and liberal RBC transfusion strategies.

##### Transfusion-related serious adverse events

One study reported transfusion-related serious adverse events.[59](#_ENREF_59) It did not find a significant difference between rates of transfusion reactions, but was underpowered for this outcome.

Clinical commentary – effect of RBC transfusion in critically ill neonatal and paediatric patients

Historically, RBC transfusions are given routinely when the Hb falls below a threshold (often 100 g/L), but this practice is based on little evidence. Although observational studies of paediatric patients demonstrate an association between RBC transfusion and mortality, causation has not been established.

The TRICC (Transfusion Requirements in Critical Care) trial provided the first clear evidence that a restrictive transfusion strategy (transfusion threshold of 70g/L) in adults may be safe. A review then showed that a restrictive transfusion strategy in adults reduced the risk of transfusion and exposure to blood products.[83](#_ENREF_83) Itfound that restrictive transfusion strategies did not affect the rate of adverse events such as mortality, pneumonia, stroke and thromboembolism. It also found that a restrictive transfusion strategy was associated with a significant reduction in in-hospital mortality.

In critically ill paediatric patients, the results of the TRIPICU trial indicate that a restrictive transfusion threshold (70 g/L) may be as safe as a liberal Hb trigger (95 g/L), and that a restrictive threshold is associated with reduced transfusion incidence.[59](#_ENREF_59) The study authors concluded that these findings could not be assumed to apply to premature infants, or to children with severe hypoxemia, haemodynamic instability, active blood loss or cyanotic heart disease, because such children were not included in the study.

Critically ill neonatal and paediatric patients with congenital heart disease, particularly cyanotic heart disease, are often transfused at Hb thresholds higher than other patients of similar age. However, there is no evidence on which to base this practice.

The CRG recommends that a restrictive transfusion strategy be employed in critically ill children (see R1).

In neonatal and paediatric patients with critical bleeding requiring massive transfusion, a critical bleeding protocol designed for these age groups should be used (Appendix K).

### 3.3 Effect of non-transfusion interventions to increase Hb concentration on outcomes

Question 2 (Interventional)

In neonates/paediatric patients, what is the effect of non-transfusion interventions to increase the Hb concentration on morbidity, mortality, and need for RBC transfusion?

Hb, haemoglobin; RBC, red blood cell

In anaemia, lower than normal levels of circulating RBCs mean a lower concentration of Hb in the blood, which leads to less oxygen circulating throughout the body, causing symptoms such as extreme tiredness, shortness of breath and dizziness. In neonates, anaemia can be associated with poor weight gain, decreased activity, tachycardia, apnoea, respiratory distress and feeding problems. In paediatric patients, anaemia may also be associated with impaired cognitive and physical development, and weakened immunity.

The review examined the effects of three interventions that aim to increase Hb concentration in neonatal and paediatric patients: erythropoiesis stimulating agents (ESAs), iron and hydroxyurea (in SCD only).

### 3.3.1 Preterm and low birth weight infants – effect of ESAs (with or without iron) on outcomes

| Evidence statements – preterm and low birth weight infants (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.1 | In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion incidence.  (See evidence matrix D2.A in Volume 2 of the technical report.) | √√√ | √ | √√ | √√ | √√√ |
| ES2.2 | In preterm infants with RhHDFN, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain.  (See evidence matrix D2.B in Volume 2 of the technical report.) | √ | NA | √√ | √√ | √ |
| ES2.3 | In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion volume.  (See evidence matrix D2.C in Volume 2 of the technical report.) | √√√ | √ | √√ | √√√ | √√√ |
| ES2.4 | In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.5 | In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on ROP is uncertain.  (See evidence matrix D2.D in Volume 2 of the technical report.) | √ | √√ | NA | √√ | √√ |
| ES2.6 | In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on BPD is uncertain.  (See evidence matrix D2.E in Volume 2 of the technical report.) | √ | √√√ | NA | √√ | √√ |
| ES2.7 | In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on NEC is uncertain.  (See evidence matrix D2.F in Volume 2 of the technical report.) | √ | √√√ | NA | √√ | √√ |
| ES2.8 | In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on mortality is uncertain.  (See evidence matrix D2.G in Volume 2 of the technical report.) | √ | √√√ | NA | √√ | √√ |
| BPD, bronchopulmonary disease; ES, evidence statement; ESA, erythropoiesis stimulating agent; NEC, necrotising enterocolitis; RhHDFN, Rh haemolytic disease of the fetus and newborn; ROP, retinopathy of prematurity √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – preterm and low birth weight infants (ESAs with or without iron) | |
| R3 (Grade C) | In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised. |
| ESA, erythropoiesis stimulating agent; R, recommendation | |

#### 

#### Background

To minimise the need for RBC transfusions, ESAs have been used to prevent or treat anaemia of prematurity. However, early studies showed that the administration of the ESA recombinant human erythropoietin (rHuEPO) can lead to iron deficiency, because blood volume expansion increases the demand for iron. Supplemental iron is therefore given in most studies assessing rHuEPO, but there are differences between studies in the dosing, timing and route of administration of iron.

#### Use of ESAs in preterm infants

The review identified six Level I studies[85-90](#_ENREF_85) and four additional Level II studies[91-94](#_ENREF_91) that examined the use of ESAs in preterm infants.

##### Transfusion incidence and volume

The two largest meta-analyses found that patients who received rHuEPO and iron required significantly fewer RBC transfusions than patients who received iron alone.[95-96](#_ENREF_95) Early rHuEPO (course of treatment commencing within the first week of life)[96](#_ENREF_96) and late rHuEPO (course of treatment commencing at 8 days or later)[95](#_ENREF_95) resulted in a significantly lower risk of receiving any transfusion compared with no rHuEPO or placebo.

rHuEPO treatment commencing in the first week also reduced the mean number of RBC transfusions per infant,[96](#_ENREF_96) but the evidence for late rHuEPO treatment was less clear.[95](#_ENREF_95)

##### Thromboembolic events

No evidence related to thromboembolic events was reported.

##### ROP

Three Level I studies assessed the effect of ESAs on ROP.[90](#_ENREF_90); [95-96](#_ENREF_95) None of the Level I studies found a significant effect of ESAs on ROP (of any level of severity), regardless of whether treatment was commenced early or late. However, a post-hoc analysis combining both early and late initiation of treatment found a significant increased risk of severe ROP (≥ stage 3) in infants who received rHuEPO.[96](#_ENREF_96)

##### BPD

Two Level I studies assessed the incidence of BPD in preterm infants administered ESAs.[95-96](#_ENREF_95) No effect was demonstrated.

##### NEC

Two Level I studies[95-96](#_ENREF_95) and one Level II study[91](#_ENREF_91) assessed the incidence of NEC in preterm infants administered ESAs. A meta-analysis of these studies performed by this review found no effect of ESAs on the incidence of NEC.

##### Mortality

Two Level I studies[85](#_ENREF_85); [96](#_ENREF_96) and one Level II study[91](#_ENREF_91) assessed the effect of ESAs on neonatal mortality. A meta-analysis performed by this review found no effect of ESAs on all-cause mortality.

##### Secondary outcomes[[2]](#footnote-2)

Functional/performance status

One systematic review[96](#_ENREF_96) assessed neurodevelopmental outcomes at 18–22 months corrected age in preterm infants administered early ESAs. Taken together, the studies were underpowered for neurodevelopmental outcomes, and the effect of ESAs on neurodevelopmental outcomes is uncertain.

Laboratory measures

Two RCTs reported laboratory measures – Hb, haematocrit (Hct) and ferritin – and found that Hb was higher in infants receiving rHuEPO.[92-93](#_ENREF_92)

Clinical commentary – ESAs (with or without iron) in preterm and low birth weight infants

This systematic review demonstrates that the number of transfusions is reduced in neonates receiving both early (course commencing within the first week of life) and late (commencing after the first week of life) rHuEPO with iron therapy. Early ESA treatment also reduced cumulative transfusion volume received, whereas the evidence for late administration of ESA was inconsistent.

There is no evidence that ESAs affect any of the following:

* mortality
* the significant neonatal morbidities ROP, BPD and NEC
* potential adverse events such as thromboembolic events.

ROP was a secondary outcome for all the included studies. It is likely that all studies were underpowered to identify true differences in ROP rates or severity. Thus, the effect of ESA therapy on ROP is uncertain. Further large RCTs are required to conclusively answer this question and address the effect of ESAs on long-term outcomes and adverse events.

Evidence of the effect of ESAs on functional and performance status is inconclusive.

Large heterogeneity was observed in the included studies, most likely reflecting variation in transfusion practice. Furthermore, the studies were mainly conducted using transfusion practice that was liberal compared to current practice, and the intervention (thrice-weekly subcutaneous injections, increased blood sampling and the need for parenteral iron) is burdensome. Therefore, the CRG has recommended against the *routine* use of ESAs (see R3).

### 3.3.2 Preterm and low birth weight infants – effect of oral and/or parenteral iron on outcomes

| Evidence statements – preterm and low birth weight infants (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.9 | In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on transfusion volume or incidence is uncertain.  (See evidence matrix D2.H in Volume 2 of the technical report.) | √√ | √ | NA | √√ | √ |
| ES2.10 | In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on ROP, BPD and NEC is uncertain.  (See evidence matrix D2.I in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √ |
| ES2.11 | In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on mortality is uncertain.  (See evidence matrix D2.J in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √ |
| BPD, bronchopulmonary disease; ES, evidence statement; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – preterm and low birth weight infants (oral and/or parenteral iron) | |
| PP13 | Preterm and low birth weight infants should receive iron supplementation as necessary to achieve the RNI. However, routine supplementation in excess of the RNI, to reduce transfusion incidence, is not supported. |
| PP, practice point; RNI, recommended nutrient intake | |

#### Background

Because of rapid growth, low iron stores at birth and losses due to blood sampling, preterm and low birth weight infants are at high risk for iron deficiency, which can impair neurodevelopment. However, due to immaturity of body organs (including the intestine and liver), they may have very limited ability to regulate iron uptake and use in response to iron deficiency or excess, particularly in the first weeks after birth.[97](#_ENREF_97) There is the potential for toxicity if excessive doses are used; enteral iron can compete with zinc and copper for absorption,[98](#_ENREF_98) 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,[99](#_ENREF_99) the safe upper limit of iron intake remains uncertain.

#### Summary of evidence

Four Level II studies examined the use of oral iron in preterm or low birth weight infants. [100-103](#_ENREF_100) No studies compared different modes of administration of iron alone or the use of parenteral iron in these groups.

##### Transfusion incidence and volume

Taylor et al (2013)[100](#_ENREF_100) compared supplemental iron to no supplemental iron in very low birth weight infants who were being fed preterm infant formula or breast milk (both of which were fortified to administer at least 2 mg/kg/day elemental iron). In another very small study, a group of infants who were mostly fed breast milk without iron fortification were randomised to receive supplemental iron or no supplemental iron.[101](#_ENREF_101) Neither study found an effect of the supplemental iron on transfusion incidence or volume. In contrast, Franz et al (2000)[103](#_ENREF_103) found a reduction in cumulative transfusion volume in (mostly breast milk fed) infants who received supplements to achieve a total iron intake of approximately 3 mg/kg/day compared to an unsupplemented group who received approximately 0.85 mg/kg/day. Berseth et al (2004)[102](#_ENREF_102) found that iron supplementation via a human milk fortifier (that aimed to provide iron intakes about 3.5 times higher than available from preterm human milk alone) reduced transfusion incidence by 15–28 days after the iron fortification was started. Despite some limited evidence that the current recommended intake of 2–3 g/kg/day elemental iron reduces the incidence of transfusion, the effect of iron therapy that provides supplementation above these intakes on transfusion volume or incidence is uncertain.

##### ROP, BPD and NEC

Three Level II studies found no significant difference in ROP, BPD and NEC between those infants (extremely low and very low birth weight) treated with additional iron and those not treated.[100-102](#_ENREF_100) However, all the studies were underpowered for these outcomes.

##### Mortality

Two Level II studies reported all-cause mortality in preterm infants with very low or extremely low birth weight but neither study was sufficiently powered to detect differences in mortality.[100](#_ENREF_100); [103](#_ENREF_103)

##### Secondary outcomes[[3]](#footnote-3)

Functional or performance status

No studies considered functional or performance status in the relevant populations.

Laboratory measures

Four Level II studies reported laboratory measures – Hb, Hct and ferritin – in preterm infants with very low or extremely low birth weight but found no significant difference reported between treatment groups.[100-103](#_ENREF_100) The section above on *Transfusion incidence and volume* explains variations in baseline iron intake.

Clinical commentary – oral and/or parenteral iron in preterm and low birth weight infants

Consistent with the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline which recommends elemental iron intakes for preterm and low birth weight infants which are currently 2–3 mg/kg/day,[104](#_ENREF_104) starting at 2–6 weeks postnatal age, the CRG advises using iron supplementation for preterm and low birth weight infants to achieve the recommended nutrient intake (RNI) or to treat any iron deficiency that is present (see PP12). The American Academy of Pediatrics’ guidelines are similar, recommending at least 2 mg/kg/day by 1 month of age.[105](#_ENREF_105)

### 3.3.3 Infants, children and adolescents at risk of anaemia – effect of ESAs (with or without iron) on outcomes

| Evidence statements – infants, children and adolescents (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.12 | In infants and children at risk of anaemia, the effect of ESA therapy (with or without iron) on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES2.13 | In infants and children at risk of anaemia, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.14 | In infants and children at risk of anaemia, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Summary of evidence

No studies compared ESAs with placebo in infants, children or adolescents with anaemia.

### 3.3.4 Infants, children and adolescents at risk of anaemia – effect of oral and/or parenteral iron on outcomes

| Evidence statements – infants, children and adolescents (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.15 | In infants and children at risk of anaemia, the effect of iron therapy compared with no iron therapy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES2.16 | In infants and children at risk of anaemia, oral iron supplementation has no effect on mortality.  (See evidence matrix D2.K in Volume 2 of the technical report.) | √√√ | √√√ | NA | √ | √ |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice points – infants, children and adolescents (oral and/or parenteral iron) | |
| PP14 | Infants and children should receive sufficient dietary iron to achieve the AI or RDI. If the AI or RDI cannot be met by dietary means, iron supplementation is advised. |
| PP15 | Infants and children in populations at high riska of iron deficiency should be screened for this condition.b  a See Domellof et al (2014)[13](#_ENREF_13) and Pottie et al (2011).[14](#_ENREF_14) b See Section 3.6. |
| PP16 | Infants and children with iron deficiency should be treated with iron supplements and dietary modifications. |
| AI, adequate intake; PP, practice point; RDI, recommended daily intake | |

#### Background

Iron deficiency is the largest factor contributing to anaemia in all paediatric age groups (except in very preterm infants in the first weeks of life, although iron deficiency is an important risk for such infants subsequently). In Australia, there is a high prevalence of iron deficiency in children from remote Indigenous communities (see Section 3.6). Risk factors for dietary iron deficiency include late introduction or insufficient iron-rich foods, prolonged exclusive breast-feeding, early introduction of cow’s milk and excessive cow’s milk consumption. Iron deficiency also occurs if there is poor gastrointestinal absorption, blood loss or increased iron requirements. Iron supplementation increases Hb and ferritin, and reduces the prevalence of iron deficiency and IDA.

Although definitive evidence is lacking, there is reasonable concern about a possible association between iron deficiency in childhood and long-term adverse neurocognitive outcomes and behavioural difficulties.[106](#_ENREF_106)

#### Summary of evidence

No studies examined the use of parenteral iron or compared different modes of administration of iron.

Two good-quality systematic reviews examined the use of oral iron in infants, children or adolescents at risk of developing anaemia.[107](#_ENREF_107)

Pasricha et al (2013)[106](#_ENREF_106) reviewed the safety and efficacy of oral iron compared to control in children aged 4–23 months on laboratory measures, growth, mortality, and functional or performance status. The review included 33 RCTs with usable data, conducted in a variety of clinical settings.

Okebe et al(2011)[107](#_ENREF_107) assessed the effect of daily oral iron supplements (with or without folic acid) compared to control in children aged under 18 years living in malaria-endemic regions. The review included 71 RCTs, and focused on outcomes of malaria, including severe malaria and mortality.

##### Mortality

Both systematic reviews reported mortality as an outcome and found no significant difference in mortality in children that received iron versus no iron.[106-107](#_ENREF_106)

##### Secondary outcomes[[4]](#footnote-4)

Functional or performance status

One Level I study reported functional and performance measures.[106](#_ENREF_106) It found no significant difference between treatment groups as assessed by the Bayley Scales of Infant and Toddler Development mental development index (MDI) or psychomotor development index (PDI). There was significant heterogeneity between the included studies. A subgroup analysis conducted to explore heterogeneity showed evidence of benefit on MDI in children with iron deficiency at baseline.

Laboratory measures

Both systematic reviews found a significant increase in Hb in children administered oral iron.[106-107](#_ENREF_106) Also, one review reported a reduced prevalence of anaemia, iron deficiency and IDA.[106](#_ENREF_106)

Clinical commentary – oral and/or parenteral iron in infants, children and adolescents at risk of anaemia

The CRG advises that infants and children should receive sufficient dietary iron to achieve the adequate intake (AI) or recommended daily intake (RDI). If the AI or RDI cannot be met by dietary means, iron supplementation is advised (see PP14).

A full blood count and ferritin should be used to screen infants and children at risk of iron deficiency (see PP15). If iron deficiency is detected, then appropriate iron supplementation and dietary modifications should be implemented (see PP16).

Oral iron supplementation at appropriate dosages, for adequate duration, is effective first-line treatment of iron deficiency in most infants, children and adolescents. Background question 5 (Section 4.5) has additional information on risk factors for iron deficiency, investigation, diagnosis and management of iron deficiency.

### 3.3.5 Medical: neonatal and paediatric patients with cancer – effect of ESAs (with or without iron) on outcomes

| Evidence statements – cancer (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.17 | In neonatal patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.18 | In paediatric patients receiving chemotherapy, ESA therapy (with or without iron) may reduce transfusion incidence.  (See evidence matrix D2.L in Volume 2 of the technical report.) | √√ | √√ | √ | √√ | √ |
| ES2.19 | In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on transfusion volume is uncertain.  (See evidence matrix D2.M in Volume 2 of the technical report.) | √ | √√ | √ | √√ | √ |
| ES2.20 | In neonatal patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.21 | In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on thromboembolic events is uncertain.  (See evidence matrix D2.N in Volume 2 of the technical report.) | √√ | NA | NA | √√ | √ |
| ES2.22 | In neonatal patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| ES2.23 | In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on mortality is uncertain.  (See evidence matrix D2.O in Volume 2 of the technical report.) | √√ | √√ | NA | √√ | √ |
| ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – cancer (ESAs with or without iron) | |
| PP17 | 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  a See R2 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| ESA, erythropoiesis stimulating agent; PP, practice point; R, recommendation | |

#### Background

Anaemia in children with cancer is a frequent occurrence, and is typically multifactorial. Bone marrow suppression may occur as a result of bone marrow infiltration or failure, chemotherapy and radiation treatments. Nephrotoxic chemotherapy may cause decreased rHuEPO production. Also, anaemia may occur as a result of blood loss secondary to thrombocytopaenia or nutritional deficiencies such as iron deficiency.

In adult cancer patients, rHuEPO has been shown to increase Hb, reduce transfusion incidence and improve quality of life; however it is associated with an increased risk of death and thromboembolic events.[3](#_ENREF_3)

#### Summary of evidence

Nine studies (Level I) examined the use of ESAs in children with cancer. The evidence from five of these studies forms the basis of this review.[108-112](#_ENREF_108) The Level I studies included six Level II studies that included patients with solid tumours or acute lymphoblastic leukaemia, and compared the use of rHuEPO with no rHuEPO.[113-119](#_ENREF_113)

##### Transfusion incidence and volume

Four RCTs reported the effect of ESAs on transfusion incidence.[114-115](#_ENREF_114); [117-118](#_ENREF_117) Meta-analysis showed that transfusion incidence was reduced in children receiving chemotherapy who were given ESA therapy.

Two small trials reported the effect of ESAs on transfusion volume.[113](#_ENREF_113); [115](#_ENREF_115) The results were conflicting.

##### Thromboembolic events

One RCT reported the incidence of thromboembolic events.[117](#_ENREF_117) It found no significant difference between those who received ESAs or placebo.

##### Mortality

Three trials reported mortality as an outcome.[115](#_ENREF_115); [117-118](#_ENREF_117) A meta-analysis of these data showed no significant difference on mortality, but the studies were small and underpowered.

##### Secondary outcomes[[5]](#footnote-5)

Functional or performance status

No evidence was identified related to functional or performance status.

Laboratory measures

Five RCTs studied the effect of ESA therapy on Hb.[113-114](#_ENREF_113); [116-118](#_ENREF_116) They reported a significant increase in Hb in children administered ESAs.

Clinical commentary – ESAs (with or without iron) in neonatal and paediatric patients with cancer

In the adult cancer population, ESAs have been demonstrated to be effective in treating cancer-induced anaemia; however, they have increased associated risks, including death and thromboembolic events.[3](#_ENREF_3)

A few small paediatric trials have suggested that use of ESAs may lead to lower transfusion requirements and improved Hb levels; however, the effect on overall survival is unknown.

In paediatric patients receiving chemotherapy, the routine use of ESAs is not advised. It is an expensive treatment and the paediatric studies are underpowered to determine their effect on mortality and thromboembolic events, which are increased in the adult population.

3.3.6 Medical: neonatal and paediatric patients with cancer – effects of oral and/or parenteral iron on outcomes

| Evidence statements – cancer (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.24 | In neonatal and paediatric patients receiving chemotherapy, the effect of iron compared with no iron on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.25 | In neonatal and paediatric patients receiving chemotherapy, the effect of iron compared with no iron on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Summary of evidence

No studies assessed the safety and efficacy of oral or parenteral iron in neonatal or paediatric cancer patients.

### 3.3.7 Medical: neonatal and paediatric patients with kidney disease – effects of ESAs (with or without iron) on outcomes

| Evidence statements – kidney disease (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.26 | In neonatal patients with kidney disease, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.27 | In paediatric patients with CKD, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.28 | In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion incidence is uncertain.  (See evidence matrix D2.P in Volume 2 of the technical report.) | X | NA | NA | √√ | √√ |
| ES2.29 | In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion volume is unknown. | NA | NA | NA | NA | NA |
| ES2.30 | In neonatal and paediatric patients with kidney disease, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.31 | In neonatal and paediatric patients with kidney disease, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| CKD, chronic kidney disease; ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice points – kidney disease (ESAs with or without iron) | |
| PP18 | In paediatric patients with CKD, 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  a See R4 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) b The KDIGO guidelines[11](#_ENREF_11) 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.  c The NICE guidelines[12](#_ENREF_12) 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). |
| PP19 | In adult patients with CKD, 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  a See R6 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP20 | ESA use is less effective in patients with CKD who have absolute or functional iron deficiency.a  a See PP13 in *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP21 | Where ESAs are indicated for the treatment or prevention of anaemia in neonatal and paediatric patients, they should be combined with iron therapy. |
| CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; PP, practice point; RBC, red blood cell; R, recommendation | |

#### Background

Anaemia is a common problem in children with chronic kidney disease (CKD) and, as glomerular filtration rate (GFR) declines, the risk of anaemia increases. In this population, anaemia is mainly due to decreased production of rHuEPO. Iron deficiency is the next most important cause of anaemia associated with kidney disease, and may result from blood loss secondary to phlebotomy, dialysis and nutritional insufficiency.

Anaemia in children with CKD is associated with increased risk of morbidity, mortality and decreased quality of life. rHuEPO and iron supplementation are used to treat anaemia associated with kidney disease.

In adults with CKD (both non-dialysis and dialysis dependent) ESAs correct anaemia, reduce the incidence of RBC transfusion and improve the quality of life of dialysis dependent patients.[3](#_ENREF_3)

#### Summary of evidence

Three systematic reviews examined the use of ESAs in children with cancer.[11](#_ENREF_11); [120-121](#_ENREF_120) However, these reviews provided no usable data.

One small Level II trial assessed the use of rHuEPO in children with acute renal failure due to haemolytic uremic syndrome.[122](#_ENREF_122)

##### Thromboembolic events

No studies reported thromboembolic events in the relevant population.

##### Mortality

No evidence was identified related to mortality.

##### Secondary outcomes[[6]](#footnote-6)

Functional or performance status

No evidence was identified related to functional or performance status.

Laboratory measures

Pape (2009)[122](#_ENREF_122) reported Hb at discharge, but the study was small and underpowered.

Clinical commentary – ESAs (with or without iron) in neonatal and paediatric patients with kidney disease

Clinical practice guidelines published by Kidney Disease Improving Global Outcomes (KDIGO)[11](#_ENREF_11) and the United Kingdom’s (UK’s) National Institute for Health and Care Excellence (NICE)[12](#_ENREF_12) assessing anaemia management in CKD noted that there is little evidence relating to the management of CKD in children. The guidelines stated that more data are needed on suitable ESA treatment regimens, and the optimal iron levels for guiding monitoring and treatment adjustments to avoid adverse outcomes.

The KDIGO guidelines[11](#_ENREF_11) suggest that, in paediatric CKD patients receiving ESA, a Hb in the range of 110–120 g/L be targeted. These guidelines recommend that all patients receiving ESAs also receive iron supplementation, to maintain a transferrin saturation of >20% and ferritin >100 mg.

The NICE guidelines[12](#_ENREF_12) advise a target Hb range of 100–120 g/L for children aged 2 years and older, and of 95–115 g/L for children aged under 2 years. They also recommend that ESAs should not be initiated in the presence of absolute iron deficiency without treating the iron deficiency.

### 3.3.8 Medical: neonatal and paediatric patients with kidney disease – effect of oral and/or parenteral iron on outcomes

| Evidence statements – kidney disease (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.32 | In neonatal and paediatric patients with kidney disease, the effect of iron compared with no iron on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.33 | In neonatal and paediatric patients with kidney disease, the effect of iron compared with no iron on mortality is unknown. | NA | NA | NA | NA | NA |
| ES2.34 | In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on transfusion incidence is uncertain.  (See evidence matrix D2.Q in Volume 2 of the technical report.) | X | NA | NA | √√ | √ |
| ES2.35 | In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.36 | In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on mortality is unknown. | NA | NA | NA | NA | NA |
| CKD, chronic kidney disease; ES, evidence statement; rHuEPO, recombinant human erythropoietin; IV, intravenous  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Summary of evidence

##### Level I evidence

One systematic review was identified; however, it contained no usable paediatric data.[123](#_ENREF_123)

One Level II study compared intravenous (IV) iron and oral iron in infants and children aged under 20 years who were on haemodialysis and receiving rHuEPO.[124](#_ENREF_124)

##### Transfusion incidence and volume

The RCTreported transfusion incidence; however, it was underpowered and no transfusions were reported in either group.[124](#_ENREF_124)

##### Thromboembolic events

No studies reported thromboembolic events in the relevant population.

##### Mortality

No evidence was identified related to mortality.

##### Secondary outcomes

Functional or performance status

No evidence was identified related to functional or performance status.

Laboratory measures

The RCT found no significant difference in Hb in children administered IV or oral iron; however, IV iron was associated with a greater increase in ferritin.[124](#_ENREF_124)

Clinical commentary – oral or parenteral iron in neonatal and paediatric patients with kidney disease

In adults with CKD, there is strong evidence that IV iron increases ferritin and transferrin saturations compared with oral iron, with only a small increase in Hb.[123](#_ENREF_123) IV iron was associated with significantly reduced ESA requirements and no significant difference in mortality.

Both the KDIGO and NICE guidelines note that there is little evidence relating to the management of CKD in children.[11-12](#_ENREF_11)

The KDIGO guidelines recommend that all paediatric patients on ESA therapy receive iron supplementation to maintain a transferrin saturation >20% and ferritin >100 mg.[11](#_ENREF_11)

The NICE guidelines recommend correcting and maintaining iron status in people with anaemia due to CKD who are receiving ESA therapy.[12](#_ENREF_12) Such patients should be offered iron therapy to achieve <6% hypochromic RBCs or a reticulocyte Hb content (or equivalent) above 29 pg (unless serum ferritin is >800 mcg/L).

The NICE guidelines also recommend that children who are iron deficient and receiving ESA therapy and haemodialysis should be offered IV iron.[12](#_ENREF_12) For children who are not receiving haemodialysis, oral iron should be considered. If the child is intolerant or the target Hb levels are not reached within 3 months, IV iron should be offered. The guidelines suggest that the approach used in children with CKD receiving ESAs (i.e. IV iron administered at a low dose and high frequency) may be more appropriate for all children.

There is no evidence and very limited experience to guide the commencement of iron supplementation and consideration of ESA therapy in neonates (<28 days of age) with severe chronic kidney disease.

### 3.3.9 Medical: neonatal and paediatric patients with SCD – effect of hydroxyurea

| Evidence statements – SCD (hydroxyurea) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.47 | In neonatal patients with SCD, the effect of hydroxyurea on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.48 | In paediatric patients with SCD, hydroxyurea decreases the incidence of transfusions.  (See evidence matrix D2.U in Volume 2 of the technical report.) | √√ | √√√ | √√ | √√√ | √√ |
| ES2.49 | In neonatal patients with SCD, the effect of hydroxyurea on stroke is unknown. | NA | NA | NA | NA | NA |
| ES2.50 | In paediatric patients with SCD, the effect of hydroxyurea on stroke is uncertain.  (See evidence matrix D2.V in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES, evidence statement; SCD, sickle cell disease  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – SCD (hydroxyurea) | |
| R4 (Grade B) | In paediatric patients with SCD, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.a, b  a Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke.  b See R1 and PP 21 |
| Practice point – SCD (hydroxyurea) | |
| PP22 | In paediatric patients over 9 months of age with SCD, hydroxyurea may be used to reduce vaso-occlusive pain crises and acute chest syndromes. |
| PP, practice point; R, recommendation; SCD, sickle cell disease; TCD, transcranial Doppler  Note: The Phase III TWiTCH trial[60](#_ENREF_60) comparing RBC transfusion to hydroxyurea in paediatric sickle cell patients was stopped early, because hydroxyurea was found to be as effective as transfusions in lowering the mean TCD velocity of blood flow. Complete data, including the secondary outcome of primary stroke, are not yet available. We await publication of the full trial results before changes to the current recommendations (R1 and R4) and practice points (PP11) are made. | |

#### Background

SCD is a condition caused by inheritance of the HbS allele, either in the homozygous form or through compound heterozygous inheritance with another beta globin gene abnormality such as HbC or beta thalassaemia. The aberrant haemoglobin (HbS) polymerises in the deoxygenated form and alters the red cell into a sickle shape. These sickled cells can get trapped in blood vessels, leading to vaso-occlusion and tissue ischaemia.

Important clinical manifestations of SCD in paediatric patients include recurrent painful vaso-occlusive episodes (e.g. dactylitis, bone pain, abdominal pain and acute chest syndrome), splenic sequestration, haemolysis, aplastic crises, priapism, infection and stroke.

Most children with SCD in developed countries will survive to adulthood; however, patients with SCD still have a significantly reduced life expectancy.

Hydroxyurea is recognised as a disease-modifying agent, and safety and efficacy in adults is well established.[125](#_ENREF_125) It has been reported to reduce vaso-occlusive crises including acute chest crises, decrease hospitalisation and improve quality of life.

#### Summary of evidence

Three systematic reviews examined the use of hydroxyurea in children with SCD, but did not provide usable data.[126-128](#_ENREF_126)

Two eligible Level II studies were identified.[129-130](#_ENREF_129) One was a small single-centre trial conducted in India, comparing hydroxyurea to placebo in 5–18 year olds with severe SCD.[129](#_ENREF_129) The other was a multi-centre trial (BABY- HUG) that assessed the safety and efficacy in hydroxyurea in infants 9 to 18 months with SCD, irrespective of severity.[130](#_ENREF_130)

##### Transfusion incidence and volume

Both studies reported a significant reduction in transfusion incidence in those children who received hydroxyurea.[129-130](#_ENREF_129)

##### Stroke

One study found no significant difference in rates of clinical stroke in a 2-year period.[130](#_ENREF_130)

##### Secondary outcomes[[7]](#footnote-7)

Functional or performance status

One study analysed neurodevelopment using the Bayley Scales of Infant and Toddler Development mental development index (MDI) and Vineland Adaptive Behaviour Scales.[130](#_ENREF_130) It reported no significant differences between treatment groups.

Laboratory measures

Both studies reported that hydroxyurea increased total Hb and fetal Hb concentrations.[129-130](#_ENREF_129)

Vaso-occlusive events and acute chest crises

One study reported that hydroxyurea decreased total painful episodes and dactylitis.[130](#_ENREF_130) Pain was nearly twice as frequent and dactylitis five times more common in children receiving placebo. The other study reported a decrease in average number of vaso-occlusive crises.[129](#_ENREF_129)

The study by Wang et al (2011)[130](#_ENREF_130) reported that hydroxyurea decreased the number of infants who experienced acute chest syndrome.

Clinical commentary – hydroxyurea in neonatal and paediatric patients with SCD

Hydroxyurea was found to be effective in reducing transfusion incidence. However, for Australian patients with SCD and their treating clinicians, reducing the incidence of transfusion may be of much less importance than the considerable effect that hydroxyurea has on reducing the frequency of vaso-occlusive crises, dactylitis, acute chest syndrome and hospitalisation. Nevertheless, the effect of hydroxyurea on reducing exposure to RBC transfusion is still of some importance, because it reduces the risk of transfusion-related adverse events, including alloimmunisation. There is a known increased risk of mild and usually reversible cytopaenias in children treated with hydroxyurea; these should be screened for and managed appropriately.

In paediatric patients with SCD who are at increased risk of stroke – as defined by elevated TCD velocities or silent infarcts seen on MRI – prophylactic RBC transfusions are recommended to reduce stroke risk. In such patients, the Phase III TWiTCH trial showed that hydroxyurea is not inferior to regular RBC transfusions in lowering mean TCD velocity.[60](#_ENREF_60) The NIH guidelines recommend that all patients with SCA and their family members be educated about hydroxyurea.[67](#_ENREF_67) In infants aged 9 months and older, and in children and adolescents with sickle cell anaemia, treatment with hydroxyurea should be offered, regardless of clinical severity of the disease, to reduce SCD-related complications such as pain, dactylitis, acute chest syndrome and anaemia.

### 3.3.10 Medical: neonatal and paediatric patients undergoing surgery – general

#### Background

Paediatric patients undergoing major surgery are at risk of blood loss and may require perioperative RBC transfusion to improve tissue oxygen delivery.

Paediatric patients undergoing elective surgery with a risk of substantial blood loss should have their full blood count and iron stores assessed preoperatively. Where preoperative anaemia is identified, it is important to determine its aetiology, so that appropriate therapy can be given.

### 3.3.11 Medical: neonatal and paediatric patients undergoing surgery – effect of ESAs (without or without iron) on outcomes

| Evidence statements – surgical (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.51 | In neonatal patients undergoing surgery, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is uncertain.  (See evidence matrix D2.W in Volume 2 of the technical report.) | X | NA | √ | √√ | √ |
| ES2.52 | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain.  (See evidence matrix D2.W in Volume 2 of the technical report.) | X | NA | √ | √√ | √ |
| ES2.53 | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on transfusion volume is unknown. | NA | NA | NA | NA | NA |
| ES2.54 | In neonatal patients undergoing cardiac surgery, the effect of ESA therapy compared with no ESA therapy on thromboembolic events is uncertain.  (See evidence matrix D2.X in Volume 2 of the technical report.) | √√ | NA | NA | √ | √ |
| ES2.55 | In neonatal patients undergoing noncardiac surgery, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.56 | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.57 | In neonatal patients undergoing cardiac surgery, the effect of ESA therapy compared with no ESA therapy on mortality is uncertain.  (See evidence matrix D2.Y in Volume 2 of the technical report.) | √√ | NA | NA | √ | √ |
| ES2.58 | In neonatal patients undergoing noncardiac surgery, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| ES2.59 | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – surgical (ESAs with or without iron) | |
| PP25 | 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. |
| ESA, erythropoiesis stimulating agent; PP, practice point | |

#### Summary of evidence

##### Three Level II studies of variable quality were identified.[131-133](#_ENREF_131) Two studies[131-132](#_ENREF_131) were conducted in the neonatal setting; the other[133](#_ENREF_133) was in infants and small children undergoing craniosynostosis repair.

##### Transfusion incidence and volume

Two trials reported the effect of ESAs on transfusion incidence or volume.[132-133](#_ENREF_132) The trials reported conflicting results; however, both trials were small and underpowered.

##### Thromboembolic events

One study reported that ESAs had no effect on the incidence of cerebral infarction and dural sinus thrombosis in neonatal cardiac surgery patients.[131](#_ENREF_131) No studies reported thromboembolic events in other infants or older children undergoing surgery.

##### Mortality

One study found no difference in mortality, but was small and underpowered.[131](#_ENREF_131) No studies reported mortality rates in other infants or older children.

##### Secondary outcomes[[8]](#footnote-8)

Functional or performance status

One study found no difference in neurodevelopmental outcomes, but was underpowered.[131](#_ENREF_131) No studies reported functional or performance measures in other infants or older children.

Laboratory measures

One study reported an increase in Hb from baseline in children undergoing craniofacical surgery who were administered rHuEPO.[133](#_ENREF_133)

### 3.3.12 Medical: neonatal and paediatric patients undergoing surgery – effect of oral and/or parenteral iron on outcomes

| Evidence statements – surgical (oral and/or parenteral iron) | | **Evidence** | **Consistency** | | | **Clinical impact** | | **Generalisability** | | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ES2.60 | In neonatal and paediatric patients undergoing surgery, the effect of iron compared with no iron on transfusion incidence or volume is unknown. | NA | | NA | NA | | NA | | NA | |
| ES2.61 | In neonatal and paediatric patients undergoing surgery, the effect of iron compared with no iron on mortality is unknown. | NA | | NA | NA | | NA | | NA | |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | | | | | |

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| --- | --- |
| Recommendation – surgical (oral and/or parenteral iron) | |
| R5  (Grade C) | In surgical paediatric patients with or at risk of IDA, preoperative iron therapy is recommended.a  a See R4 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| Practice points – surgical (oral and/or parenteral iron) | |
| PP23 | In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiencya should be identified, evaluated and managed to minimise RBC transfusion.b  a Iron deficiency can be present with a normal Hb. b See Appendix G (*Paediatric haemoglobin assessment and optimisation template*) for further information on the optimal dosing strategy. |
| PP24 | To implement PP23, 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. |
| Hb, haemoglobin; IDA, iron deficiency anaemia; PP, practice point; R, recommendation; RBC, red blood cell | |

#### Summary of evidence

No studies reviewed the safety and efficacy of oral or IV iron in neonatal or paediatric patients undergoing surgery.

Clinical commentary ­– oral or parenteral iron in neonatal and paediatric patients undergoing surgery

With the paucity of evidence in the paediatric surgical setting, a recommendation was based on the evidence from the adult literature.[2](#_ENREF_2)

### 3.3.12 Critically ill term and near term neonatal patients[[9]](#footnote-9) and paediatric patients – general

#### Background

Critically ill neonates and children admitted to the ICU are at high risk of receiving a red cell transfusion, often in the setting of stable anaemia.

Neonatal and paediatric patients are at risk of anaemia in the critical care setting because of the physiological anaemia of newborns, smaller blood volumes, proportionally higher phlebotomy losses from blood testing and discard volumes (central venous access and arterial lines), surgical related blood loss and malnutrition.

Iron is one of the main regulators of erythropoiesis; therefore, low iron stores and nutritional intake may limit Hb recovery. ESAs promote the bone marrow production of RBCs.

Although RBC transfusions may be associated with risk and morbidity, in the adult population, alternatives to transfusion such as ESA therapy are not without complications.

### 3.3.13 Critically ill term and near term neonatal patients and paediatric and patients – effect of ESAs, with or without iron, on outcomes

| Evidence statements – critically ill (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.62 | In critically ill neonatal patients, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.63 | In critically ill paediatric patients, the effect of ESA therapy plus iron compared with iron alone on transfusion volume or incidence is uncertain.  (See evidence matrix D2.Z in Volume 2 of the technical report.) | √ | √√√ | NA | √√ | √ |
| ES2.64 | In critically ill neonatal and paediatric patients, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES2.65 | In critically ill paediatric patients with acute respiratory failure, the effect of ESA therapy plus iron compared with iron alone on mortality is uncertain.  (See evidence matrix D2.AA in Volume 2 of the technical report.) | √ | NA | NA | √√ | √ |
| ES2.66 | In critically ill neonatal patients, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – critically ill (ESAs with or without iron) | |
| PP26 | In critically ill paediatric patients with anaemia, ESAs should not be *routinely* used.a  a This point is based on the lack of effect of ESAs on mortality in critically ill adult patients. See R2 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[4](#_ENREF_4) |
| ESA, erythropoiesis stimulating agent; PP, practice point; R, recommendation | |

#### Summary of evidence

Two Level II trials of poor and fair quality examined the use of ESAs in critically ill paediatric patients.[134-135](#_ENREF_134)

##### Transfusion incidence and volume

Both trials reported transfusion incidence.[134-135](#_ENREF_134) A meta-analysis of these studies showed no significant difference in incidence of RBC transfusions or mean transfusions per patient.

One study reported that ESA treatment did not alter transfusion volume.[135](#_ENREF_135) However, our re-analysis using the results reported in the paper indicated a significant benefit of rHuEPO with iron for reducing the volume of RBC transfused.

##### Thromboembolic events

No trials assessed the incidence of thromboembolic events.

##### Mortality

One trial reported mortality rates.[135](#_ENREF_135) No deaths occurred in either treatment arm.

##### Secondary outcomes[[10]](#footnote-10)

Functional or performance status

No studies reported functional or performance status.

Laboratory measures

Both studies reported laboratory measures – Hct and ferritin – but with conflicting results.[134-135](#_ENREF_134)

### 3.3.14 Critically ill term and near term neonatal patients and paediatric patients – effect of oral and/or parenteral iron, on outcomes

| Evidence statements – critically ill (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES2.67 | In critically ill neonatal and paediatric patients, the effect of iron compared with no iron on transfusion incidence or volume is unknown. | NA | NA | NA | NA | NA |
| ES2.68 | In critically ill neonatal and paediatric patients, the effect of iron compared with no iron on mortality is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – critically ill (oral and/or parenteral iron) | |
| PP27 | Critically ill paediatric patients should receive iron supplementation as necessary to achieve the RNI. |
| PP, practice point; RNI, recommended nutrient intake | |

#### Summary of evidence

No studies assessed the use of oral or IV iron in critically ill neonatal or paediatric patients.

Clinical commentary – oral or parenteral iron in critically ill term and near term neonatal patients and paediatric patients

It is important that critically ill neonatal and paediatric patients continue to receive sufficient dietary iron to achieve the adequate intake (AI) or recommended daily intake (RDI). If the AI or RDI cannot be met by dietary means, iron supplementation is advised.

## 3.4 Effect of blood components on outcomes

Question 3 (Interventional)

In paediatric/neonate patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

#### Background

The systematic review examined the evidence for five interventions in neonatal and paediatric patients: fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate and platelet transfusion.

FFP contains all the coagulation factors present in normal plasma and is primarily transfused in the neonatal and paediatric setting to correct abnormalities of coagulation.

The administration of FFP has been associated with a range of side effects including infection, allergic reactions, haemolysis, TACO and TRALI. Therefore, the risks and benefits of FFP transfusion need to be carefully considered before use.

Cryoprecipitate is administered to patients to correct hypofibrinogenaemia. Primary triggers for transfusion of cryoprecipitate include:

haemostatic support during massive blood loss

low fibrinogen and active bleeding before or during an invasive procedure

dysfibrinogenaemia (structural abnormalities of the fibrinogen molecule that cause dysfunction)

active bleeding before or during an invasive procedure.

Fibrinogen may also be administered to patients with hypofibrinogenaemia.[[11]](#footnote-11)

Platelet transfusions are frequently used to correct thrombocytopaenia in critically ill patients. The use of platelet transfusion has been associated with a range of side effects including bacterial infection (due to contamination), allergic reactions, febrile reactions, venous thromboembolism, TRALI and TACO. Therefore, the risks and benefits of platelet transfusion in critically ill patients need to be carefully considered before use. Primarytriggers for transfusion of platelets are:

low platelet count and active bleeding before or during an invasive procedure

prophylaxis after chemotherapy

bone marrow transplant

known or suspected disorder (acquired or inherited) affecting platelet function

active bleeding before or during an invasive procedure.

Overall, two Level I studies, six Level II studies and seven Level III studies were identified in the systematic review.

The search identified no literature specifically pertaining to Australia’s Aboriginal and Torres Strait Islander peoples relevant to this research question.

### 3.4.1 Preterm and low birth weight infants – effects of FFP on outcomes

| Evidence statements – preterm and low birth weight infants (FFP) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.1 | In preterm (<32 weeks) or very low birth weight infants (<1500 g), the effect of FFP compared with no FFP on mortality is uncertain.  (See evidence matrix D3.A in Volume 2 of the technical report.) | √ | √√√ | NA | √√√ | √ |
| ES3.2 | In preterm (<32 weeks) or very low birth weight infants (<1500 g), the effect of FFP compared with no FFP on IVH is uncertain.  (See evidence matrix D3.B in Volume 2 of the technical report.) | √ | √√ | NA | √√√ | √ |
| ES3.3 | In preterm (<37 weeks) infants, the effect of FFP compared with no FFP on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.4 | In preterm (<37 weeks) infants, the effect of FFP compared with no FFP on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.5 | In preterm (<37 weeks) infants, the effect of FFP compared with a different FFP transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.6 | In preterm (<37 weeks) infants, the effect of FFP compared with a different FFP transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.7 | In preterm (<37 weeks) infants, the effect of FFP compared with a different FFP transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.8 | In preterm (<37 weeks) infants, the effect of FFP compared with a different FFP transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma; IVH, intraventricular haemorrhage  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – preterm and low birth weight infants (FFP) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

##### Level I evidence

One good-quality Level 1 study that included four Level II studies was identified.[136](#_ENREF_136)

The review included 940 preterm infants of very low birth weight or born at or before 32 weeks gestation, and who were less than 72 hours old. The authors examined the effect of volume expansion using FFP compared with a control group (no treatment) on mortality and peri/intraventricular haemorrhage (P/IVH).

##### Level II evidence

One Level II study that was conducted by the Northern Neonatal Nursing Initiative (NNNI) was retrieved for further analysis.[137](#_ENREF_137) This was a fair-quality multicentre RCT conducted in 18 UK maternity units that recruited 776 preterm infants born less than 32 weeks gestation. The three-armed trial compared the effect of prophylactic FFP (20 ml/kg followed by 10 ml/kg after 24 hours) or an inert gelatin plasma substitute (Gelofusine) to a maintenance infusion of 10% dextrose (control). Outcomes included mortality and P/IVH at 6 weeks.

Mortality

The Level I study[136](#_ENREF_136) assessed the incidence of mortality in preterm infants administered FFP compared with no FFP or placebo in a meta-analysis of three RCTs and found no difference between treatment groups.

The Level II study[137](#_ENREF_137) found no difference in mortality before 6 weeks or before discharge, or in cause-specific mortality before discharge attributed to respiratory distress, IVH, necrotising enterocolitis or other causes.

There was a follow-up of survivors from the first NNNI trial, 2 years after the intervention.[138](#_ENREF_138) Subgroup analyses were performed for cause-specific mortality in infants aged 1–23 months. There was no significant difference in mortality due to chronic lung disease, sudden unexpected death, infection or other causes.

##### Bleeding events

A meta-analysis of 120 preterm infants born before 32 weeks gestation found no difference in incidence of P/IVH in infants administered FFP P/IVH (any grade) compared with a no-treatment control group.[136](#_ENREF_136) There was also no significant difference in P/IVH (any grade) and P/IVH grade 2–4; however, the comparisons were both underpowered.

The initial NNNI trial[137](#_ENREF_137) also found that, among scanned infants surviving 6 weeks, there was no significant difference in IVH (any grade), subependymal IVH or severe IVH.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – use of FFP in preterm and low birth weight infants

The limited information available suggests that the routine administration of FFP has no effect on mortality and on prevention of IVH in preterm infants. Nevertheless, FFP may have a role in the treatment of clinical bleeding where coagulopathy is a contributing factor. When prescribing FFP, both risks and benefits should be considered.

### 3.4.2 Preterm and low birth weight infants – effects of platelet transfusion on outcomes

| Evidence statements – preterm and low birth weight infants (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.9 | In preterm (<32 weeks) or extremely low birth weight (<1000 g) infants, the effect of platelet transfusion compared with no platelet transfusion on mortality is uncertain.  (See evidence matrix D3.C in Volume 2 of the technical report.) | √ | √√ | X | √√ | √ |
| ES3.10 | In neonates with thrombocytopaenia admitted to NICU, platelet transfusion may be associated with an increased risk of IVH compared with no platelet transfusion.  (See evidence matrix D3.D in Volume 2 of the technical report.) | √ | √√√ | X | √√ | √ |
| ES3.11 | In preterm (<37 weeks) infants, the effect of platelet transfusion compared with no platelet transfusion on bleeding events other than IVH is unknown. | NA | NA | NA | NA | NA |
| ES3.12 | In preterm (<37 weeks) infants, the effect of platelet transfusion compared with no platelet transfusion on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.13 | In preterm (<37 weeks) infants, the effect of platelet transfusion compared with no platelet transfusion on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – preterm and low birth weight infants (platelet transfusion) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified three Level III cohort studies comparing platelet transfusion strategies in neonatal and paediatric patients:

A good-quality retrospective cohort study of 1600 neonates with thrombocytopaenia in multiple NICUs, conducted in the United States of America (USA).[139](#_ENREF_139) The study investigated the effect of platelet transfusion versus no platelet transfusion on mortality.

A poor-quality nested case–control study in a single NICU in the USA of 164 preterm infants born at or before 32 weeks gestation.[140](#_ENREF_140) Cases were defined as participants with thrombocytopaenia (platelet count ≤150 × 109/L) and controls as those without thrombocytopaenia. Of the 94 included cases, 12 were defined as having mild thrombocytopaenia (100–150 × 109/L), 34 with moderate (50–100 109/L), and 48 with severe (<50 × 109/L). The authors examined whether platelet transfusion had an effect on IVH by days 7 and 14 of life, sepsis, NEC, thrombocytopaenia-associated bleeding and mortality before discharge.

A poor-quality retrospective cohort study of 284 extremely low birth weight (≤1000 g) preterm infants from multiple NICUs in the USA.[141](#_ENREF_141) The authors examined the effect of platelet transfusion on mortality during and after thrombocytopaenia. Data were collected from electronic medical records, case mix, pharmacy and laboratory systems.

##### Mortality

The good-quality study found a significant increase (apparently dose dependent) in mortality associated with platelet transfusion.[139](#_ENREF_139) The nested study also found a significant increase in mortality associated with platelet transfusion.[140](#_ENREF_140) In contrast, the third study demonstrated no association between mortality and platelet transfusion.[141](#_ENREF_141)

##### Bleeding events

One study[139](#_ENREF_139) demonstrated a significant increase in severe IVH (grade 3–4) associated with platelet transfusion. Similarly, one study[140](#_ENREF_140) demonstrated a significant increase in IVH associated with platelet transfusion.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

### 3.4.3 Preterm and low birth weight infants – effects of platelet transfusion using a different transfusion strategy on outcomes

| Evidence statements – preterm and low birth weight infants (platelet transfusion using a different platelet transfusion strategy) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.14 | In preterm infants (<32 weeks), the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on mortality is uncertain.  (See evidence matrix D3.E in Volume 2 of the technical report.) | √ | NA | NA | √√√ | √√ |
| ES3.15 | In preterm (<32 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on bleeding events is uncertain.  (See evidence matrix D3.F in Volume 2 of the technical report.) | √ | NA | NA | √√ | √√ |
| ES3.16 | In preterm (<37 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.17 | In preterm (<37 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on RBC transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma; NICU, neonatal intensive care unit; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – preterm and low birth weight infants (platelet transfusion) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified one fair-quality Level III study, conducted in two NICUs in the Netherlands.[142](#_ENREF_142) It included 679 premature infants born before 32 weeks gestation, and examined the effect of restrictive platelet transfusion (transfused when active haemorrhage and platelet count <50 × 109/L) compared with liberal platelet transfusion (transfused according to predefined platelet count threshold) on mortality, IVH (all grades) and major haemorrhage.

##### Mortality

The study found no significant difference in overall mortality between restrictive and liberal platelet transfusion groups.[142](#_ENREF_142)

##### Bleeding events

In infants with cranial ultrasounds available, the study found no significant difference in IVH incidence in preterm infants allocated to a restrictive or liberal platelet transfusion strategy.[142](#_ENREF_142) In a subgroup analysis of thrombocytopaenic patients, there was no significant difference in IVH (grade 1 or 2) or severe IVH (grade 3 or 4).

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – platelet transfusion in preterm and low birth weight infants

Platelet transfusion is often used in severely thrombocytopaenic preterm infants to prevent or treat IVH or other active bleeding. However, there is no clear evidence of benefit or harm from this treatment. The appropriate threshold for platelet transfusion will depend on clinical circumstances. Suggested thresholds for stable patients range from 20 to 50 × 109/L. For the appropriate platelet threshold for prevention of bleeding, results of a large RCT are awaited.[143](#_ENREF_143) When prescribing platelet transfusion, both risks and benefits should be considered.

### 3.4.4 Paediatric patients with cancer – effects of platelet transfusion on outcomes

| Evidence statements – cancer (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.18 | In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.19 | In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.20 | In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.21 | In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.22 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on mortality is uncertain.  (See evidence matrix D3.G in Volume 2 of the technical report.) | X | NA | NA | √√ | √ |
| ES3.23 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on significant bleeding events is uncertain.  (See evidence matrix D3.H in Volume 2 of the technical report.) | X | NA | NA | √√ | √ |
| ES3.24 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.25 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on the incidence of platelet transfusions is uncertain.  (See evidence matrix D3.I in Volume 2 of the technical report.) | X | NA | NA | √√ | √ |
| ES3.26 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on the incidence of RBC transfusions is unknown. | NA | NA | NA | NA | NA |
| ES3.27 | In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on transfusion volume is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice points – cancer (platelet transfusion) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| PP29 | For guidance on the use of FFP in specific patient groups, refer to:a   * *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)*[1](#_ENREF_1) * *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*[2](#_ENREF_2) * *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*[15](#_ENREF_15) * AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) * *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*.[16](#_ENREF_16)   a See PP17 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| PP30 | 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 × 109/L in the absence of risk factors, and at <20 × 109/L in the presence of risk factors (e.g. fever, minor bleeding).a  a See R8 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| AHCDO, Australian Haemophilia Centre Directors' Organisation; FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

##### Level I evidence

One good-quality Level I study was identified.[144](#_ENREF_144) Of the 13 studies included in the review, two were in solely paediatric populations and involved children hospitalised with previously untreated acute myeloid leukaemia or acute lymphoblastic leukaemia.[145-146](#_ENREF_145) Only one study met our inclusion criteria.[146](#_ENREF_146) The review authors rated this study as having an overall unclear risk of bias.

The study by Murphy et al (1982)[146](#_ENREF_146) investigated the effect of therapeutic platelet transfusions (administered only in presence of bleeding) compared with a prophylactic platelet transfusion, administered to maintain platelet count above 20 × 109/L, on all- mortality (from all causes and bleeding).

##### Mortality

The study reported no significant difference on mortality overall and due to bleeding; however, it was underpowered.[146](#_ENREF_146)

##### Bleeding events

The study found no significant difference between therapeutic platelet transfusion administered in the presence of bleeding compared with prophylactic platelet transfusion administered to maintain platelet count above 20 × 109/L on children with ≥1 significant bleeding event (patients with acute myeloid leukaemia or acute lymphoblastic leukaemia).[146](#_ENREF_146)

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

The study found no significant difference between therapeutic platelet transfusion administered in the presence of bleeding and prophylactic platelet transfusion administered to maintain platelet count above 20 × 109/L on mean number of platelet transfusions per course of chemotherapy.[146](#_ENREF_146)

Clinical commentary – platelet transfusion in paediatric patients with cancer

Given the lack of reliable evidence in paediatric patients of the effect of prophylactic platelet transfusion, it is reasonable to use evidence from adult patients (see PP29). This is consistent with two new sets of guidelines applicable to children.[147-148](#_ENREF_147)

### Neonatal and paediatric patients undergoing surgery – effects of FFP on outcomes

| Evidence statements – surgical (FFP) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.28 | In paediatric liver transplant patients, any association between FFP transfusion and mortality is uncertain.  (See evidence matrix D3.J in Volume 2 of the technical report.) | √ | NA | X | √√√ | √√ |
| ES3.29 | In paediatric patients undergoing surgery other than liver transplant, the effect of FFP compared with no FFP on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.30 | In neonatal patients undergoing surgery, the effect of FFP compared with no FFP on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.31 | In neonatal and paediatric patients undergoing cardiac surgery, the use of an FFP-based pump priming fluid compared with an albumin-based fluid does not reduce postoperative blood loss.  (See evidence matrix D3.K in Volume 2 of the technical report.) | √ | √√ | NA | √√ | √ |
| ES3.32 | In neonatal and paediatric patients undergoing noncardiac surgery, the effect of FFP compared with no FFP on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.33 | In neonatal and paediatric patients undergoing surgery, the effect of FFP compared with no FFP on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.34 | In neonatal and paediatric patients undergoing cardiac surgery, the use of an FFP-based pump priming fluid compared with an albumin-based fluid does not reduce intraoperative or postoperative transfusion volume or incidence.  (See evidence matrix D3.L in Volume 2 of the technical report.) | √ | √√ | NA | √√√ | √ |
| ES3.35 | In neonatal and paediatric patients undergoing noncardiac surgery the effect of FFP compared with no FFP on transfusion volume and incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.36 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.37 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.38 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.39 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on transfusion volume and incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- | --- |
| Recommendation – surgical (FFP) | | |
| R6 (Grade C) | | 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. |
| Practice points – surgical (FFP) | | | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. | | |
| PP29 | For guidance on the use of FFP in specific patient groups, refer to:a   * *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)*[1](#_ENREF_1) * *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*[2](#_ENREF_2) * *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*[15](#_ENREF_15) * AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) * *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*.[16](#_ENREF_16)   a See PP17 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) | | |
| Expert opinion point – surgical (FFP) | | | |
| EOP1 | | 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 POC or laboratory testing. | |
| AHCDO, Australian Haemophilia Centre Directors’ Organisation; EOP, expert opinion point; FFP, fresh frozen plasma; POC, point-of-care; PP, practice point; R, recommendation | | | |

#### Summary of evidence

The literature search identified three eligible Level II studies:

a fair-quality RCT of 123 paediatric patients aged 1 month to 16 years who required cardiac surgery with CPB[149](#_ENREF_149)

a fair-quality RCT of 20 infants weighing less than 8 kg who required CPB surgery[150](#_ENREF_150)

a poor-quality RCT of 56 paediatric patients weighing 10 kg or less who required CPB surgery.[151](#_ENREF_151)

One eligible Level III study was identified.[73](#_ENREF_73) This was a fair-quality retrospective cohort study in 243 paediatric liver transplant patients aged <18 years.

##### Mortality

In the Level II study, a multivariate cox regression model did not demonstrate any association between mortality and postoperative FFP administration. [73](#_ENREF_73) In a propensity score adjusted analysis, no association between intraoperative FFP use and mortality was observed.

##### Bleeding events

The Level II studies of FFP in pump prime reported no significant difference in bleeding events.[149-150](#_ENREF_149)

In a secondary analysis, one poor-quality RCT[151](#_ENREF_151) reported a significant reduction in postoperative blood loss in complex surgery patients (p=0.003) and cyanotic patients (p=0.035) that favoured FFP.[143](#_ENREF_143)

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

In one Level II study, infants and children who received 1–2 units of FFP in the pump prime required a significantly greater volume of blood intraoperatively (p=0.001), and significantly more RBCs in the CPB circuit (p=0.002) and after heparin reversal (p=0.047).[149](#_ENREF_149) However, patients who received FFP in the pump prime required significantly less FFP after heparin reversal (p=0.042). Another Level II study reported that total blood products transfused intraoperatively and 24 hours postoperatively were significantly higher in patients who received 1 unit of FFP in the pump prime (p=0.035).[151](#_ENREF_151)

In contrast, the third demonstrated a reduction blood product administration following the use of FFP in the pump prime for infants undergoing cardiac surgery (p=0.05).[150](#_ENREF_150) However, in a subgroup analysis only the use of cryoprecipitate was significantly lower in infants who received FFP (p<0.0001). There was no significant difference for RBCs or platelets.

Clinical commentary – FFP in neonatal and paediatric patients undergoing surgery

The effect of the routine use of FFP on mortality, bleeding and transfusion incidence and volume in neonatal and paediatric patients undergoing surgery is unclear. Hence, this treatment should be reserved for treatment of bleeding where coagulopathy is a contributing factor. Both the risks and benefits of administration of FFP should be considered.

### 3.4.6 Neonatal and paediatric patients undergoing surgery – effects of cryoprecipitate on outcomes

| Evidence statements – surgical (cryoprecipitate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.40 | In neonatal and paediatric patients undergoing surgery, the effect of cryoprecipitate compared with no cryoprecipitate on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.41 | In neonatal and paediatric patients undergoing surgery, the effect of cryoprecipitate compared with no cryoprecipitate on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.42 | In neonatal and paediatric patients undergoing surgery, the effect of cryoprecipitate compared with no cryoprecipitate on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.43 | In neonatal and paediatric patients undergoing surgery, the effect of cryoprecipitate compared with no cryoprecipitate on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.44 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal cryoprecipitate transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.45 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal cryoprecipitate transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.46 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal cryoprecipitate transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.47 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal cryoprecipitate transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Practice point – surgical (cryoprecipitate) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| Expert opinion point – surgical (cryoprecipitate) | |
| EOP2 | 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 groups.a  a The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation. |
| EOP, expert opinion point ; FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified no studies in the relevant population.

##### Mortality

No evidence was identified related to mortality.

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – cryoprecipitate in neonatal and paediatric patients undergoing surgery

Cryoprecipitate should be used to treat bleeding in the setting of hypofibrinogenaemia. There is no clear threshold for clinically significant hypofibrinogenaemia.[152](#_ENREF_152) However, in actively bleeding patients, it is reasonable to aim for a fibrinogen level of >1.5 g/L. A target level of >2 g/L may be appropriate in certain patients; for example, those with major trauma, those receiving large transfusion volumes and neonates.

### 3.4.7 Neonatal and paediatric patients undergoing surgery – effects of platelets on outcomes

| Evidence statements – surgical (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.48 | In paediatric liver transplant patients, the effect of platelet transfusion compared with no platelet transfusion on mortality is uncertain.  (See evidence matrix D3.M in Volume 2 of the technical report.) | X | NA | NA | √√√ | √√ |
| ES3.49 | In paediatric patients undergoing surgery other than liver transplant, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.50 | In neonatal patients undergoing surgery, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.51 | In neonatal and paediatric patients undergoing surgery, the effect of platelet transfusion compared with no platelet transfusion on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.52 | In neonatal and paediatric patients undergoing surgery, the effect of platelet transfusion compared with no platelet transfusion on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.53 | In neonatal and paediatric patients undergoing surgery, the effect of platelet transfusion compared with no platelet transfusion on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.54 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal platelet transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.55 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal platelet transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.56 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal platelet transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.57 | In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal platelet transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – surgical (platelet transfusion) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| Expert opinion point – surgical (platelet transfusion) | |
| EOP3 | In general, neonatal and paediatric patients with a platelet count ≥ 50 × 109/L *or* an INR ≤2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts and higher INRs may be tolerated.a  a See PP17 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| EOP, expert opinion point; FFP, fresh frozen plasma; INR, international normalised ratio; PP, practice point | |

#### Summary of evidence

The review identified one eligible Level III study.[73](#_ENREF_73) This was a fair-quality retrospective cohort study of 243 paediatric liver transplant patients aged <18 years from deceased brain-dead donors. The authors examined the effect on mortality of different doses of preoperative, perioperative and postoperative platelet transfusions.

##### Mortality

The study found no significant difference in mortality at 1 year for intraoperative platelet transfusion (≥1 unit) or postoperative platelet transfusion (≥1 unit) compared with no transfusion.[73](#_ENREF_73) The authors also found no significant difference in mortality between three doses of preoperative platelet transfusion (p=0.929).

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – use of platelets in neonatal and paediatric patients undergoing surgery

Given the lack of reliable evidence in paediatric patients undergoing surgery of the effect of platelet transfusion, it is reasonable to use evidence from adult patients. A preoperative platelet count threshold of 50 × 109/L is suggested (see EOP3). A higher threshold may be appropriate where risk of bleeding is high, or in selected patients (e.g. 100 × 109/L in those undergoing neuraxial surgery or ocular surgery).

Prophylactic platelets may also be indicated in the presence of platelet dysfunction, depending on the severity of the dysfunction but regardless of the platelet count.

### Neonatal and paediatric patients undergoing surgery – effects of fibrinogen concentrate on outcomes

| Evidence statements – surgical (fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.58 | In paediatric liver transplant patients, the effect of a higher volume of preoperative fibrinogen concentrate compared with a lower volume of preoperative fibrinogen concentrate on mortality is uncertain.  (See evidence matrix D3.N in Volume 2 of the technical report.) | √ | NA | NA | √√ | √ |
| ES3.59 | In paediatric patients undergoing surgery other than liver transplant, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.60 | In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.61 | In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.62 | In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.63 | In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| CPB, cardiopulmonary bypass; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – surgical (fibrinogen concentrate) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

One Level I study was identified that evaluated the safety and effectiveness of fibrinogen concentrate in bleeding patients.[153](#_ENREF_153) The analysis included both adult and paediatric populations, and thus did not provide any usable data.

The review identified one eligible Level III study that examined the effect of fibrinogen concentrate in paediatric patients: a fair-quality retrospective cohort study of 243 paediatric liver transplant patients aged less than 18 years.[73](#_ENREF_73)

##### Mortality

The study demonstrated no significant difference in mortality at 1 year between three doses of fibrinogen concentrate (p=0.308).[73](#_ENREF_73)

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

### Neonatal and paediatric patients undergoing surgery – effects of use of a different fibrinogen strategy on outcomes

| Evidence statements – surgical (fibrinogen concentrate using a different fibrinogen strategy) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.64 | In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.65 | In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on mortality is uncertain.  (See evidence matrix D3.O in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √ |
| ES3.66 | In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on bleeding events is uncertain.  (See evidence matrix D3.P in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √ |
| ES3.67 | In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.68 | In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.69 | In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, fibrinogen concentrate compared with cryoprecipitate may reduce transfusion incidence.  (See evidence matrix D3.Q in Volume 2 of the technical report.) | √√ | NA | X | √√√ | √ |
| ES3.70 | In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on transfusion volume is unknown. | NA | NA | NA | NA | NA |
| ES3.71 | In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| CPB, cardiopulmonary bypass; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – surgical (fibrinogen concentrate using a different fibrinogen strategy) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified one good-quality RCT at a single hospital in Brazil.[154](#_ENREF_154) It included 63 children aged under 7 years who underwent cardiac surgery with CPB, and examined the effect of fibrinogen concentrate (60 mg/kg) compared with cryoprecipitate (10 mL/kg) on mortality, bleeding, transfusion requirements and thromboembolic events. The authors noted that limitations of the study included the small sample size and single-centre design.

##### Mortality

The study reported no deaths in the cohort.[154](#_ENREF_154)

##### Bleeding events

The study found no significant difference in 48-hour blood loss (intraoperative and 46-hour drainage) between fibrinogen concentrate and cryoprecipitate (p=0.672).

##### Transfusion related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

The study found a significant difference in postoperative transfusion incidence between children who received fibrinogen concentrate (86.7%) and those who received cryoprecipitate (100.0%) (p=0.046).[154](#_ENREF_154)

##### Secondary outcomes

Thromboembolic events

The study found no significant difference in any thromboembolic event, including stroke, acute myocardial infarction, deep venous thrombosis and pulmonary embolism.[154](#_ENREF_154)

Clinical commentary ­– use of fibrinogen in neonatal and paediatric patients undergoing surgery

Fibrinogen concentrate has been shown to be a safe and effective treatment for correction of hypofibrinogenaemia with a low rate of serious adverse events. In other countries, it is used exclusively as a replacement for cryoprecipitate. However, it is not currently licensed for use in any setting other than genetic deficiency.

### Neonatal and paediatric patients undergoing surgery – effects of combination therapy on outcomes

| Evidence statements – surgical (combination FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.72 | In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.73 | In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.74 | In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.75 | In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| --- | --- |
| Practice point – surgical (combination therapy) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified no eligible studies.

##### Mortality

No evidence was identified related to mortality.

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – combination therapy in neonatal and paediatric patients undergoing surgery

Combined use of cryoprecipitate, platelets and FFP may be appropriate in settings where there is active bleeding and evidence of coagulopathy and thrombocytopaenia (or platelet dysfunction). Use should be guided by clinical assessment in association with viscoelastometric POC testing or laboratory results (or both).

### Critically ill neonatal and paediatric patients – effects of FFP on outcomes

| Evidence statements – critically ill (FFP) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.76 | In critically ill neonatal and paediatric patients, the effect of FFP compared with no FFP on mortality is uncertain.  (See evidence matrix D3.R in Volume 2 of the technical report.) | √ | √√ | X | √√ | √√ |
| ES3.77 | In critically ill neonatal and paediatric patients, the effect of FFP compared with no FFP on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.78 | In critically ill neonatal and paediatric patients, the effect of FFP compared with no FFP on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.79 | In critically ill neonatal and paediatric patients, the effect of FFP compared with no FFP on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.80 | In critically ill neonatal and paediatric patients, the effect of FFP compared with a different FFP transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.81 | In critically ill neonatal and paediatric patients, the effect of FFP compared with a different FFP transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.82 | In critically ill neonatal and paediatric patients, the effect of FFP compared with a different FFP transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.83 | In critically ill neonatal and paediatric patients, the effect of FFP compared with a different FFP transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice points – critically ill (FFP) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| PP29 | For guidance on the use of FFP in specific patient groups, refer to:a   * *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)*[1](#_ENREF_1) * *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*[2](#_ENREF_2) * *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*[15](#_ENREF_15) * AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) * *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*.[16](#_ENREF_16)   a See PP17 from *Patient Blood Management Guidelines: Module 3 – Medical*.[3](#_ENREF_3) |
| AHCDO, Australian Haemophilia Centre Directors’ Organisation; FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

This review identified two eligible Level III studies that examined the effect of FFP compared with no FFP in critically ill paediatric patients, both of good quality:

a retrospective analysis of 315 paediatric patients with acute lung injury in two PICUs in the USA that compared mortality and ventilation outcomes among patients who received FFP and those who did not[155](#_ENREF_155)

a prospective cohort study conducted at a single PICU in Canada that included 831 paediatric intensive care patients aged under 18 years, and examined the effect of FFP on a number of clinical outcomes including mortality.[156](#_ENREF_156)

##### Mortality

In a multivariate analysis adjusted for paediatric risk of mortality (PRISM III) scores, one study demonstrated no significant association between FFP transfusion and mortality (p=0.09).[155](#_ENREF_155) In the other study, although a mortality rate of 16.0% was reported in those children administered FFP and 1.8% in those not given FFP, the effect was not significant after adjusting for potential confounders.[156](#_ENREF_156)

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – effects of FFP in critically ill neonatal and paediatric patients

There is limited evidence on the effect of the routine use of FFP in critically ill neonatal and paediatric patients. FFP use should be reserved for the treatment of active bleeding where coagulopathy is a contributing factor. Careful consideration of the risks and benefits of platelets in this setting is advised.

### 3.4.12 Critically ill neonatal and paediatric patients – effects of cryoprecipitate on outcomes

| Evidence statements – critically ill (cryoprecipitate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.84 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with no cryoprecipitate on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.85 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with no cryoprecipitate on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.86 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with no cryoprecipitate on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.87 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with no cryoprecipitate on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.88 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with a different cryoprecipitate transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.89 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with a different cryoprecipitate transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.90 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with a different cryoprecipitate transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.91 | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with a different cryoprecipitate transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – critically ill (cryoprecipitate) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

No eligible studies were identified.

##### Mortality

No evidence was identified related to mortality.

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary ­– effects of cryoprecipitate in critically ill neonatal and paediatric patients

Cryoprecipitate should be used to treat active bleeding in the setting of hypofibrinogenaemia. There is no clear threshold for clinically significant hypofibrinogenaemia.[152](#_ENREF_152) However, it is reasonable to aim for a fibrinogen level of >1.5 g/L. A target level of >2 g/L may be appropriate in certain patients; for example, neonates and those receiving large transfusion volumes.

### Critically ill neonatal and paediatric patients – effects of platelets on outcomes

| Evidence statements – critically ill (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.92 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with no platelet transfusion on mortality is uncertain.  (See evidence matrix D3.S in Volume 2 of the technical report.) | √ | NA | NA | √√ | √ |
| ES3.93 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with no platelet transfusion on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.94 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with no platelet transfusion on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.95 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with no platelet transfusion on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.96 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with a different platelet transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.97 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with a different platelet transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.98 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with a different platelet transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.99 | In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with a different platelet transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – critically ill (platelet transfusion) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

The review identified one good-quality Level III study: a retrospective analysis of 315 paediatric patients with acute lung injury in two PICUs in the USA.[155](#_ENREF_155) The authors compared mortality and ventilation outcomes among patients who received platelets and those who did not.

##### Mortality

In a multivariate analysis, no difference in mortality was observed.[155](#_ENREF_155)

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – platelet transfusion in critically ill neonatal and paediatric patients

Prophylactic platelet transfusion is often used in neonates and paediatric patients with critical illness. However, there is limited evidence in this patient group and it is therefore reasonable to apply evidence from studies in adult patients.

Suggested thresholds are:

* in stable patients without bleeding, 10 × 109/L
* in a nonbleeding patient with risk factors (sepsis, renal failure, medications) for bleeding, 20 × 109/L
* in patients undergoing invasive procedures, 50 × 109/L.

In patients in whom there is active bleeding, higher thresholds may be appropriate.

For perioperative patients, see Section 3.4.7.

For patients with FNAIT, see section 4.1.5.

Careful consideration of the risks and benefits of platelets in critically ill neonatal and paediatric patients is advised. Platelet transfusions are not indicated in all cases of thrombocytopaenia, and may be contraindicated or ineffective in certain conditions (e.g. in immune thrombocytopaenia , thrombotic thrombocytopaenia purpura and heparin-induced thrombocytopaenia).

### Critically ill neonatal and paediatric patients – effects of fibrinogen concentrate on outcomes

| Evidence statements – critically ill (fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.100 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.101 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.102 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.103 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES3.104 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with a different fibrinogen concentrate transfusion strategy on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.105 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with a different fibrinogen concentrate transfusion strategy on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.106 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with a different fibrinogen concentrate transfusion strategy on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.107 | In critically ill neonatal and paediatric patients, the effect of fibrinogen concentrate compared with a different fibrinogen concentrate transfusion strategy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – critically ill (fibrinogen concentrate) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

This review identified no eligible studies for this population.

##### Mortality

No evidence was identified related to mortality.

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – fibrinogen concentrate in critically ill neonatal and paediatric patients

Fibrinogen concentrate has been shown to be a safe and effective treatment for correction of hypofibrinogenaemia with a low rate of serious adverse events. In other countries, it is used exclusively as a replacement for cryoprecipitate.[[12]](#footnote-12)[[13]](#footnote-13)

### Critically ill neonatal and paediatric patients – effects of combination therapy on outcomes

| Evidence statements – critically ill (combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES3.108 | In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on mortality is unknown. | NA | NA | NA | NA | NA |
| ES3.109 | In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES3.110 | In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion-related serious adverse events is unknown. | NA | NA | NA | NA | NA |
| ES3.111 | In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; FFP, fresh frozen plasma  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice point – critically ill (combination therapy) | |
| PP28 | In neonatal and paediatric patients, the decision to transfuse cryoprecipitate, FFP, fibrinogen concentrate and 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. |
| FFP, fresh frozen plasma; PP, practice point | |

#### Summary of evidence

This review identified no eligible studies for this population.

##### Mortality

No evidence was identified related to mortality.

##### Bleeding events

No evidence was identified related to bleeding events.

##### Transfusion-related serious adverse events

No studies reported transfusion-related serious adverse events.

##### Transfusion volume or incidence

No studies reported transfusion volume or incidence.

Clinical commentary – combination therapy in critically ill neonatal and paediatric patients

Combined use of cryoprecipitate, platelets and FFP may be appropriate in settings where there is active bleeding and evidence of coagulopathy and thrombocytopaenia (or platelet dysfunction). Use should be guided by clinical assessment in association with viscoelastometric POC testing or laboratory results (or both).

## 3.5 Use of blood conservation strategies

Question 4 (Interventional)

In neonates/paediatric patients, what is the effect of strategies that minimise blood loss and/or reduce the need for RBC transfusion?

RBC, red blood cell

Neonatal and paediatric patients have smaller absolute blood volumes and red cell mass than older patients. Therefore, depletion of RBCs through blood loss or haemolysis can have a proportionately greater influence on the patient’s subsequent incidence of transfusion.

Many hospitalised neonatal and paediatric patients are at risk of blood loss, which places them at risk for transfusion. Three populations were considered for Question 4: preterm and term infants needing neonatal intensive care, neonatal and paediatric patients undergoing surgery, and critically ill neonatal and paediatric patients.

The following interventions were considered for their potential to improve outcomes and reduce transfusion requirements:

two specific to neonates:

placental transfusion to increase the circulating blood volume and red cell mass

intravenous immunoglobulin (IVIg) to reduce haemolysis in infants born with neonatal alloimmune haemolysis (widely known as haemolytic disease of the fetus and newborn (HDFN)

several pertaining to all neonatal and paediatric patients undergoing surgery:

prevention of hypothermia

controlled induced hypotension compared with no induced hypotension

acute normovolaemic haemodilution (ANH)

intraoperative cell salvage

viscoelastometric point-of-care (POC) testing

antifibrinolytics

recombinant activated factor VII (rFVIIa) (cardiac and extracorporeal membrane oxygenation [ECMO] patients only)

miniaturised CPB systems compared with standard-sized systems

two interventions for critically ill paediatric patients were assessed:

rFVIIa compared with no rFVIIa (cardiac and ECMO patients only)

viscoelastometric POC testing.

The search identified no literature specifically pertaining to Australia’s Aboriginal and Torres Strait Islander peoples relevant to this research question.

### 3.5.1 Preterm and term infants – effects of placental transfusion on outcomes

| Evidence statements – preterm and term infants (placental transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.1 | In preterm infants, placental transfusion compared with no placental transfusion may reduce transfusion volume and incidence.  (See evidence matrix D4.A in Volume 2 of the technical report.) | √ | √√√ | √√ | √√ | √√ |
| ES4.2 | In preterm and term infants, the effect of placental transfusion compared with no placental transfusion on mortality is uncertain.  (See evidence matrix D4.B in Volume 2 of the technical report.) | √ | √ | NA | √√ | √√ |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Practice points – preterm and term infants (placental transfusion) | |
| PP31 | In preterm infants, deferring cord clamping for between 30 seconds and 3 minutes may reduce transfusion volume and incidence, and incidence of IVH. 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. |
| PP32 | In term infants, deferring cord clamping for at least 1 minute is likely to reduce the risk of iron deficiency at 3–6 months. This intervention should be considered in infants who do not require active resuscitation, provided that access to phototherapy for jaundice is available.a  a See McDonald et al (2013)[19](#_ENREF_19) |
| IVH, intraventricular haemorrhage; PP, practice point | |

#### Background

In newborn infants, the number of RBCs in circulation decreases after birth. Infants born before term have an exaggerated decrease in Hb due to several factors, including loss of RBCs due to shortened red cell survival and frequent withdrawal of blood, reduced erythropoietin response to anaemia due to immaturity and, in some cases, severity of illness. In addition, rapid growth – faster in the second and early third trimester of pregnancy than at any other time of life – contributes to anaemia of prematurity. Placental transfusion may provide the infant with additional blood volume and RBCs, and thus protect against such anaemia. The amount of blood returned to the infant depends on when the cord is clamped. There is uncertainty about whether the level at which the infant is held (above or below the mother’s abdomen) before clamping is important.[157-158](#_ENREF_157)

#### Summary of evidence

This review identified five relevant Level I studies of varying quality.[19](#_ENREF_19); [159-162](#_ENREF_159) Two studies were of good quality, and provided the most comprehensive evidence for preterm infants.[159](#_ENREF_159); [162](#_ENREF_162) The included Level I studies assessed 20 Level II studies that reported outcomes relevant to the research question. This systematic review identified two additional Level II studies.[163-164](#_ENREF_163)

Transfusion incidence and volume

This review performed a meta-analysis to evaluate all studies (including the two additional RCTs identified). The analysis showed that placental transfusion significantly reduced the incidence of RBC transfusions and the mean number of RBC transfusions. No significant differences in transfusion volume were reported in any of the included studies.

Mortality

An updated meta-analysis that evaluated the effect of placental transfusion on mortality in preterm infants demonstrated no significant difference in mortality following placental transfusion.

IVH

This review performed a meta-analysis that included all identified RCTs and that assessed the effect of placental transfusion in preterm infants on IVH (all grades) grouped by gestational age at birth. The analyses showed a significant effect favouring placental transfusion on the incidence of IVH (all grades) but not severe IVH.

Clinical commentary – placental transfusion in preterm and term infants

In preterm infants, deferred cord clamping appears to reduce the incidence of subsequent transfusion, through mechanisms that may include increasing blood volume at birth or decreasing severity of illness. However, concerns remain about the risks and benefits of routinely deferring cord clamping for all preterm infants. These concerns can be summarised as follows.

*Trial quality and selection bias.* The evidence in relation to preterm infants comprises a number of small, underpowered trials of variable quality. The inclusion and exclusion criteria varied, but several studies specifically excluded multiple births, infants born by caesarean section and infants who were compromised in utero or were judged to be depressed at birth. These are clinically and numerically important subgroups of preterm births.

*High transfusion rates in the included studies.* The incidence of transfusion in <32 week infants in this review was 49% in the group who had deferred cord clamping or cord milking to achieve placental transfusion, and 66% in the immediate cord clamping group. A population-based study in New South Wales, where deferred cord clamping was not routinely practised, identified a transfusion rate of 33%.[165](#_ENREF_165) These findings suggest that more restrictive transfusion strategies, or other practices in Australian neonatal units that affect transfusion incidence, will result in a smaller effect of deferred cord clamping on subsequent transfusion than is indicated by this review.

*Timing of cord clamping in relation to onset of breathing.* The published randomised trials have not taken onset of breathing into account as a potential confounder. Trials are underway to address some of the considerable uncertainty that remains as to the balance of risks and benefits in infants who do not start to breathe effectively within the first 30–60 seconds after birth, in relation to whether:

* deferred cord clamping should take precedence over manoeuvres to support breathing or not
* assisted ventilation (and other resuscitation steps, if needed) can and should be provided while the cord remains unclamped
* cord milking (either before clamping the cord or from a long segment of cord that remains attached to the baby) is a safe and effective alternative to deferred cord clamping.

This review found that the effect of deferred cord clamping on mortality is uncertain, but there was a benefit in reducing IVH (of any grade). However, the effect of deferred cord clamping on other neurodevelopmental outcomes, particularly longer term outcomes, remains unknown.

### 3.5.2 Preterm and term infants – effects of IVIg for haemolytic disease on outcomes

| Evidence statements – haemolytic disease (IVIg) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.3 | In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on exchange transfusion incidence is uncertain.  (See evidence matrix D4.C in Volume 2 of the technical report.) | √√ | √√ | NA | √√√ | √ |
| ES4.4 | In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on mortality is uncertain.  (See evidence matrix D4.D in Volume 2 of the technical report.) | √√ | √√√ | NA | √√√ | √ |
| ES, evidence statement; IVIg, intravenous immunoglobulin  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – haemolytic disease (IVIg) | |
| R7  (Grade B) | In infants with HDFN, the *routine* use of IVIg is not recommended. |
| Practice point – haemolytic disease (IVIg) | |
| PP33 | Infants at risk of HDFN should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. |
| Expert opinion point – haemolytic disease (IVIg) | |
| EOP4 | In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. |
| EOP, expert opinion point; HDFN, haemolytic disease of the fetus and newborn; IVIg, intravenous immunoglobulin; PP, practice point, R, recommendation | |

#### Background

Haemolytic disease of the fetus and newborn (HDFN) is characterised by a breakdown of RBCs by maternal antibodies. During pregnancy, some of the mother’s antibodies are transported across the placenta and enter the fetal circulation. Antibodies to the RhD, Rhc and Kell antigen are the most common causes of severe HDFN in Australia.

Anaemia is the most significant problem in utero (see Section 4.2.1) because excess fetal bilirubin crosses the placenta and is eliminated by the mother. However, bilirubin levels can rise rapidly after birth, leading to the need for intensive phototherapy and exchange transfusion. Exchange transfusions are associated with an increased risk of neonatal morbidity and mortality. Since IVIg can compete with alloantibodies for Fc receptors on cells that mediate RBC breakdown,[166](#_ENREF_166) it has been proposed that it can reduce the incidence of exchange transfusion.

#### Summary of evidence

One good-quality Level I study that included 12 RCTs was identified.[167](#_ENREF_167) No additional Level II studies were identified.

##### Exchange transfusion incidence

The systematic review assessed the effect of IVIg on the incidence of exchange transfusion in term and preterm neonates with HDFN secondary to Rh or ABO incompatibility.[167](#_ENREF_167) It performed separate meta-analyses in Rh and ABO incompatible patients. A significant reduction in exchange transfusion incidence following IVIg was reported (p<0.00001); however, in a sensitivity analysis that included only RCTs assessed to have an overall low risk of bias, the significant difference was not observed (p=0.37). In a subanalysis of RCTs involving preterm neonates only, there was no significant difference between treatment groups for the incidence of exchange transfusions.

The review also assessed number of exchange transfusions per infant.[167](#_ENREF_167) A sensitivity analysis of RCTs assessed to have an overall low risk of bias found no significant difference on the number of exchange transfusions per infant.

##### Mortality

No deaths were reported in the included studies.[167](#_ENREF_167)

Clinical commentary – IVIg for haemolytic disease in preterm and term infants

Administering IVIg to newborns has been postulated to reduce the severity of haemolysis with HDFN. The combined results of all trials suggest that IVIg can reduce the incidence of exchange transfusion (ET) in infants with HDFN; however, the earlier trials were generally of low quality.[167](#_ENREF_167) When only the trials at low risk of bias were considered, there was no effect of IVIg on reducing incidence of ET or any other outcome of importance (e.g. peak bilirubin, duration of phototherapy or need for top-up transfusion). None of the trials was powered to assess rare (but potentially life-threatening) adverse effects such as TRALI, the risk of which is likely to increase with transfusion of plasma products. The recent, high-quality trials specified the use of intensive phototherapy, which is the most effective neonatal treatment to reduce the need for ET.

Although the review suggested a benefit of IVIg in reducing ET for jaundice due to ABO incompatibility, the studies were also of low quality.[167](#_ENREF_167) It seems unlikely that IVIg would be of benefit in ABO haemolysis (which is typically milder) if there is no benefit in RhD HDFN. With the availability of intensive phototherapy, ABO incompatibility has become an increasingly uncommon indication for ET in Australia.[168](#_ENREF_168) It is a rare cause of top-up transfusion.[169](#_ENREF_169)

### 3.5.3 Neonatal and paediatric patients undergoing surgery – effects of prevention of hypothermia on outcomes

| Evidence statements – surgical (prevention of hypothermia) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.5 | In paediatric patients undergoing cardiac surgery with CPB, the effect of preventing hypothermia compared with no prevention of hypothermia on mortality is uncertain.  (See evidence matrix D4.E in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES4.6 | In paediatric patients undergoing noncardiac surgery, the effect of preventing hypothermia compared with no prevention of hypothermia on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.7 | In paediatric patients undergoing cardiac surgery with CPB, the effect of preventing hypothermia compared with no prevention of hypothermia on transfusion volume or incidence is uncertain.  (See evidence matrix D4.F in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√ |
| ES4.8 | In paediatric patients undergoing noncardiac surgery, the effect of preventing hypothermia compared with no prevention of hypothermia on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| CPB, cardiopulmonary bypass; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Recommendation – surgical (prevention of hypothermia) | |
| R8  (Grade B) | In paediatric patients undergoing surgery, measures to prevent hypothermia should be used.a  a See R12 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| R, recommendation | |

#### Background

Prevention of hypothermia in patients undergoing surgery is an important part of good perioperative care. Anaesthesia alters thermoregulatory mechanisms, which can lead to hypothermia if active warming techniques are not used. Even mild hypothermia can cause adverse effects in adult surgical patients, including substantial increases in adverse cardiac outcomes, surgical blood loss, allogeneic transfusion and surgical site infections (see Section 3.6.2 and R12 in Module 2 (*Perioperative*)[2](#_ENREF_2)). Up to 20% of adult surgical patients experience unintended perioperative hypothermia, defined as a core temperature below 36°C. Paediatric patients are more vulnerable to perioperative hypothermia because they have a reduced weight-to-surface-area ratio, lower stores of subcutaneous fat and greater loss of heat from the head compared with adults; hence, they require a vigilant proactive approach to maintenance of normothermia.

#### Summary of evidence

One good-quality Level II study was identified: an RCT of 59 paediatric patients undergoing cardiac surgery with CPB.[170](#_ENREF_170) The authors examined the effect of normothermia (body temperature maintained at 35–37°C) compared with hypothermia (body temperature maintained at 28°C) on all-cause in-hospital mortality, and RBC transfusion volume and incidence.

Mortality

The study assessed all-cause mortality among 59 paediatric patients undergoing cardiac surgery with CPB.[170](#_ENREF_170) No deaths were recorded during the study, but it was underpowered for this outcome.

Transfusion volume and incidence

The study assessed transfusion volume (mL/kg) and incidence among 59 paediatric patients undergoing cardiac surgery with CPB.[170](#_ENREF_170) No significant differences between groups were reported for RBC transfusion incidence and median RBC transfusion volume (9.6 versus 9.5).

Clinical commentary – prevention of hypothermia in neonatal and paediatric patients undergoing surgery

Based on the good evidence in the adult population, active measures to prevent unintentional hypothermia in children are recommended. It is unlikely that RCTs examining the effects of hypothermia on RBC transfusion in children would be ethically acceptable.

### 3.5.4 Neonatal and paediatric patients undergoing surgery – effects of prevention of controlled induced hypotension on outcomes

| Evidence statements – surgical (deliberate/controlled induced hypotension) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.9 | In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.10 | In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on transfusion incidence is uncertain.  (See evidence matrix D4.G in Volume 2 of the technical report.) | X | NA | NA | √√ | √√ |
| ES4.11 | In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on transfusion volume is unknown. | NA | NA | NA | NA | NA |
| ES4.12 | In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on bleeding events is uncertain.  (See evidence matrix D4.H in Volume 2 of the technical report.) | X | NA | √ | √√ | √√ |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Background

Controlled induced hypotension involves deliberately lowering a patient's mean arterial blood pressure to below normal, aiming to limit blood loss or improve the surgical field. In paediatrics, its use is common in scoliosis surgery.

#### Summary of evidence

One poor-quality Level II study was identified.[171](#_ENREF_171) The study enrolled 50 adolescent patients aged 13–15 years who were undergoing osteotomy or genioplasty.

Transfusion volume or incidence

No studies reported transfusion volume or incidence..

Bleeding events

A significant difference favouring induced hypotension was reported for estimated blood loss by surgeon and by the anaesthetist. A significant difference favouring induced hypotension was also reported for average estimated blood loss and surgical field rating.

Clinical commentary – controlled induced hypotension in neonatal and paediatric patients undergoing surgery

There is little evidence on safety and efficacy to guide the use of controlled induced hypotension in paediatric surgery. It is difficult to extrapolate evidence from the adult population to the paediatric population, because the types of surgery where controlled induced hypotension is advantageous in adults are not relevant in paediatrics.

In spinal surgery, the use of controlled hypotension needs to be balanced against the risk of causing reduced perfusion of the spinal cord and other organs.

### 3.5.5 Neonatal and paediatric patients undergoing surgery – effects of ANH on outcomes

| Evidence statements – surgical ANH) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.13 | In paediatric patients undergoing surgery, the effect of ANH compared with no ANH on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.14 | In paediatric patients undergoing surgery, the effect of ANH compared with no ANH on transfusion volume and incidence is uncertain.  (See evidence matrix D4.I in Volume 2 of the technical report.) | √ | √√√ | NA | √√ | √√ |
| ANH, acute normovolaemic haemodilution; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Practice point – surgical (ANH) | |
| PP34 | In paediatric patients, ANH has not been shown to reduce transfusion or improve clinical outcomes. However, if ANH 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. |
| ANH, acute normovolaemic haemodilution; PP, practice point | |

#### Background

ANH is a blood conservation technique that aims to reduce allogeneic transfusion requirements in patients scheduled for elective surgery. For the purposes of this review, ANH was defined as the removal of a patient’s blood shortly after induction of anaesthesia, with maintenance of normovolaemia using crystalloid or colloid replacement, then reinfusion of the patient’s blood during or shortly after surgery. This autologous whole blood (which is kept at room temperature) has a greater concentration of better functioning platelets and clotting factors than banked blood. Hence, it may be helpful in correcting coagulopathy as well as improving Hct and decreasing the risk of allogeneic transfusion.

In infants, particularly those aged under 6 months, there may be greater safety issues with ANH because of their inability to compensate for acute anaemia or blood loss.

#### Summary of evidence

The systematic review identified three Level II studies that examined the safety and effectiveness of ANH in paediatric patients undergoing surgery**:**

one of fair quality, conducted in paediatric patients undergoing cardiac surgery[172](#_ENREF_172)

one of poor quality, conducted in paediatric patients undergoing craniofacial repair surgery[173](#_ENREF_173)

one of poor quality, studying adolescents undergoing surgery for scoliosis concentration.[174](#_ENREF_174)

Mortality

No studies reported the effect of ANH on mortality in neonatal and paediatric patients undergoing surgery.

Transfusion volume and incidence

Friesen et al (2006)[172](#_ENREF_172) reported no significant difference in RBC transfusion incidence during surgery with CPB or after surgery with CPB.[172](#_ENREF_172)

Hans et al (2000)[173](#_ENREF_173) assessed transfusion volume and incidence in 34 paediatric patients scheduled for surgical repair for scaphocephaly or pachycephaly. No significant difference was reported for transfusion incidence or transfusion volume.

Lisander et al (1996)[174](#_ENREF_174) assessed transfusion volume in 23 adolescents undergoing scoliosis surgery and found no significant difference in the number of donor blood units transfused.

Clinical commentary – ANH in neonatal and paediatric patients undergoing surgery

There is little evidence on the use of ANH in paediatric surgery; therefore, the effect on transfusion incidence or volume is uncertain. If this technique is used, a local procedural guideline needs to be in place to ensure patient safety (see R14 and PP12 in Module 2 (*Perioperative*)[2](#_ENREF_2)).

### 3.5.6 Neonatal and paediatric patients undergoing surgery – effects of intraoperative cell salvage on outcomes

| Evidence statements – surgical (intraoperative cell salvage) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.15 | In paediatric patients undergoing cardiac surgery with CPB, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on mortality is uncertain.  (See evidence matrix D4.J in Volume 2 of the technical report.) | √√ | √√√ | NA | √√√ | √ |
| ES4.16 | In paediatric patients undergoing noncardiac surgery, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.17 | In paediatric patients undergoing cardiac surgery with CPB, intraoperative cell salvage compared with no intraoperative cell salvage may reduce transfusion volume and incidence.  (See evidence matrix D4.K in Volume 2 of the technical report.) | √ | √√ | √ | √√√ | √ |
| ES4.18 | In paediatric patients undergoing noncardiac surgery, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on transfusion volume and incidence is uncertain.  (See evidence matrix D4.K in Volume 2 of the technical report.) | X | NA | NA | √ | √√ |
| CPB, cardiopulmonary bypass; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Practice point – surgical (intraoperative cell salvage) | |
| PP35 | In paediatric patients undergoing cardiac surgery with CPB, 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. |
| CPB, cardiopulmonary bypass; PP, practice point | |

#### Background

Intraoperative cell salvage involves collection of blood lost during surgery. In patients undergoing CPB, the residual volume of blood in the circuit can also be salvaged. The collected blood is then mixed with an anticoagulant solution containing either heparin or citrate to prevent clotting. As blood enters the collection reservoir, it is filtered to remove large particulate debris. Before salvaged blood can be reinfused back into the patient, it must be centrifuged and washed to produce RBCs suspended in saline.

#### Summary of evidence

This review identified three Level II studies: one of good quality[175](#_ENREF_175) and two of poor quality.[174](#_ENREF_174); [176](#_ENREF_176)

Mortality

None of the three included studies were sufficiently powered to detect any difference in mortality.

Transfusion volume and incidence

Cholette et al (2013)[175](#_ENREF_175) assessed transfusion needs among 106 children scheduled for cardiac surgery with CPB. Cell salvage (including use of residual CPB circuit volume) reduced the mean number of RBCs transfused within 24 hours post-surgery and 48 hours post-surgery; however, the effect did not remain statistically significant at 7 days post-surgery. In this study, the cell saver blood was safely stored and used for 24 hours after collection.

Lisander et al (1996)[174](#_ENREF_174) reported no significant difference in the mean number of donor blood units transfused among 24 adolescents undergoing surgery for scoliosis. Being a pilot, this study was not powered to assess differences in clinical outcomes.

Ye et al (2013)[176](#_ENREF_176) assessed the median volume of perioperative allogeneic RBC transfused in 309 paediatric patients scheduled for open heart surgery with CPB and reported a significant effect favouring cell salvage (1.5 versus 2.5, p=0.000).

Clinical commentary – intraoperative cell salvage in neonatal and paediatric patients undergoing surgery

Limited evidence in paediatric cardiac surgical patients undergoing CPB suggests a reduction in RBC transfusion incidence and coagulant product administration, and fewer donor exposures in the first 48 hours in the cell salvage group. Further studies are required before the routine use of this technique could be advised (see R15 and PP13 in Module 2 (*Perioperative*)[2](#_ENREF_2)).

### 3.5.7 Neonatal and paediatric patients undergoing surgery – effects of viscoelastometric POC testing on outcomes

| Evidence statements – surgical (viscoelastometric POC testing) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.19 | In paediatric patients undergoing surgery, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.20 | In paediatric patients undergoing surgery, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES4.21 | In paediatric patients undergoing surgery, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; POC, point of care  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Practice point – surgical (viscoelastometric POC testing) | |
| PP36 | In paediatric patients undergoing cardiac surgery with CPB, viscoelastometric POC testing may be considered. |
| CPB, cardiopulmonary bypass; POC, point of care; PP, practice point | |

#### Background

Viscoelastometric POC testing includes thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These tests measure clot development, stabilisation and dissolution (fibrinolysis), which reflect in vivo haemostasis. In paediatric patients undergoing surgery, these techniques offer improvements over traditional laboratory testing in the assessment of bleeding patients.

#### Summary of evidence

This review identified no eligible studies.

Clinical commentary – viscoelastometric POC testing in neonatal and paediatric patients undergoing surgery

One small RCT that evaluated the use of viscoelastometric POC testing in paediatric patients undergoing cardiac surgery with CPB was published after the cut-off date of this systematic review.[177](#_ENREF_177) The study demonstrated a reduction in postoperative transfusion requirements with algorithm-guided blood product management that included viscoelastometric POC testing. Further studies are required to clarify the role of this technology.

### 3.5.8 Neonatal and paediatric patients undergoing surgery – effects of antifibrinolytics on outcomes

| Evidence statements – surgical (antifibrinolytics) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.22 | In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on mortality is uncertain.  (See evidence matrix D4.L in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √ |
| ES4.23 | In paediatric patients undergoing cardiac surgery, antifibrinolytics compared with no antifibrinolytics reduce transfusion volume and incidence.  (See evidence matrix D4.M in Volume 2 of the technical report.) | √√ | √√ | √ | √√ | √ |
| ES4.24 | In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume.  (See evidence matrix D4.N in Volume 2 of the technical report.) | √√ | √√ | √ | √√√ | √√ |
| ES4.25 | In paediatric patients undergoing surgery for scoliosis, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain.  (See evidence matrix D4.N in Volume 2 of the technical report.) | √√ | √√ | NA | √√√ | √√ |
| ES4.26 | In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume.  (See evidence matrix D4.O in Volume 2 of the technical report.) | √√ | √√ | √ | √√ | √√ |
| ES4.27 | In paediatric patients undergoing craniofacial surgery, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain.  (See evidence matrix D4.O in Volume 2 of the technical report.) | √√ | √√ | NA | √√ | √√ |
| ES4.28 | In paediatric patients undergoing primary adenoidectomy, the effect of topical TXA compared with no TXA on transfusion incidence is uncertain.  (See evidence matrix D4.P in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √ |
| ES4.29 | In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on thromboembolic events is uncertain.  (See evidence matrix D4.Q in Volume 2 of the technical report.) | √√ | √√√ | NA | √√ | √ |
| ES4.30 | In paediatric patients undergoing cardiac surgery, the effect of antifibrinolytics compared with no antifibrinolytics on postoperative blood loss in uncertain.  (See evidence matrix D4.R in Volume 2 of the technical report.) | √ | √ | NA | √√ | √ |
| ES4.31 | In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics may reduce blood loss.  (See evidence matrix D4.S in Volume 2 of the technical report.) | √√ | √√ | √ | √√√ | √√ |
| ES4.32 | In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics reduce perioperative blood loss.  (See evidence matrix D4.T in Volume 2 of the technical report.) | √√ | √√√ | √ | √√ | √ |
| ES4.33 | In paediatric patients undergoing ENT surgery, antifibrinolytics compared with no antifibrinolytics may reduce perioperative blood loss.  (See evidence matrix D4.U in Volume 2 of the technical report.) | √√ | √√ | X | √√ | √ |
| ENT, ear, nose and throat; ES, evidence statement; TXA, tranexamic acid  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Recommendation – surgical (antifibrinolytics) | |
| R9  (Grade B) | In paediatric patients undergoing cardiac surgery with CPB, the routine use of antifibrinolytics is recommended.a  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. |
| R10  (Grade C) | In paediatric patients undergoing surgery for scoliosis in whom substantial blood loss is anticipated, the use of antifibrinolytics should be considered.  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. |
| R11  (Grade C) | In paediatric patients undergoing craniofacial surgery in whom substantial blood loss is anticipated, the use of antifibrinolytics should be considered.  a TXA in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. EACA is not licensed for use in Australia. |
| Practice points – surgical (antifibrinolytics) | |
| PP37 | In acutely bleeding critically ill paediatric trauma patients, tranexamic acid should be administered within 3 hours of injury.a  See R3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*[4](#_ENREF_4) |
| PP38 | In paediatric trauma patients under 12 years of age, a tranexemic 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.a  a See the template given in Appendix K (*Critical bleeding protocol*), which is intended for local adaptation. |
| CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; PP, practice point; R, recommendation; TXA, tranexamic acid | |

#### Background

Antifibrinolytics such as aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) may reduce perioperative bleeding by inhibiting fibrin degradation.

Aprotinin inhibits fibrinolysis by inactivation of plasmin and other proteolytic enzymes. Before 2007, aprotinin was commonly used in both cardiac surgery and major noncardiac surgery to reduce blood loss and blood transfusion. However, it was withdrawn from the market following the release of results from the Blood Conservation Using Antifibrinolytics in a Randomised Trial (BART), which showed that in high-risk adult cardiac surgical patients undergoing complex cardiac surgery, mortality was higher with aprotinin than with lysine analogues. This finding resulted in the early termination of this study. However, there has been subsequent criticism of the design of the BART and controversy over its findings.

Aprotinin remains on the Australian Register of Therapeutic Goods but is not being supplied or marketed by the Australian sponsor.

TXA inhibits the activation of plasminogen to plasmin, thus reducing fibrin degradation. The use of TXA is recommended in adult patients undergoing cardiac surgery or noncardiac surgery in which significant blood loss is anticipated. TXA tablets and solution for injection are approved in Australia for a number of indications including cardiac surgery, traumatic hyphaema and patients with coagulopathy undergoing minor surgery.

EACA reduces fibrinolysis by inhibiting proteolytic enzymes. It reduces allogeneic blood transfusion in adult cardiac surgery patients. However, it is not available or licensed for use in Australia.

#### Summary of evidence

Six Level I studies that assessed the safety and effectiveness of antifibrinolytics (aprotinin, TXA or EACA) in paediatric patients undergoing surgery were identified.[178-183](#_ENREF_178) A further two Level I studies[184-185](#_ENREF_184) were identified in the review but did not provide any data additional to the included Level I studies. Thirty included Level II studies reviewed the evidence for the use of antifibrinolytics in paediatric patients undergoing a variety of surgeries including cardiac, scoliosis, craniofacial, and ear, nose and throat (ENT) surgery.

*Cardiac surgery* – Three good-quality Level I studies provided the evidence for paediatric patients undergoing cardiac surgery.[178-179](#_ENREF_178); [181](#_ENREF_181) One assessed aprotinin in paediatric patients aged under 18 years with CHD undergoing open heart surgery with CPB.[178](#_ENREF_178) It included 12 RCTs involving 626 infants and children. The other assessed TXA in paediatric patients aged under 18 years undergoing cardiac surgery and included data from eight RCTs involving 848 infants and children.[179](#_ENREF_179)

*Scoliosis surgery* – One good-quality Level I study provided evidence for the effect of antifibrinolytics (aprotinin, TXA or EACA) in paediatric patients undergoing scoliosis surgery.[183](#_ENREF_183)

*Craniofacial surgery* – One fair-quality Level I study provided evidence for the effect of antifibrinolytics in paediatric patients undergoing craniofacial surgery.[182](#_ENREF_182)

*ENT surgery* – One good-quality Level I study assessed the effect of topical administration of TXA in patients of any age undergoing ENT surgery.[180](#_ENREF_180) It identified 29 RCTs, only one of which was in paediatric patients. It enrolled 400 children undergoing primary isolated adenoidectomy and provided evidence for the effect of TXA in ENT surgery on transfusion incidence and blood loss.

The systematic review identified 12 Level II studies, additional to the 30 Level II studies identified and assessed by the included Level I studies. Those studies were in patients undergoing either cardiac, scoliosis, craniofacial or ENT surgery.

Seven additional Level II studies provided evidence for paediatric patients undergoing cardiac surgery.[186-192](#_ENREF_186) All were fair to poor quality.

Two additional Level II studies provided evidence for paediatric patients undergoing scoliosis surgery, one of poor quality[193](#_ENREF_193) and one of good quality.[194](#_ENREF_194)

Two additional Level II studies provided evidence for paediatric patients undergoing craniofacial surgery: a fair-quality RCT[195](#_ENREF_195) and a good-quality RCT.[196](#_ENREF_196)

Two additional Level II studies provided evidence for paediatric patients undergoing ENT surgery: a good-quality RCT and a fair-quality RCT.[197](#_ENREF_197)

##### Mortality

Cardiac surgery

No included study reported a significant difference in mortality.

Scoliosis surgery

No deaths were reported in the included studies.

Craniofacial surgery

No deaths were reported in the included studies.

ENT surgery

No deaths were reported in the included study.

##### Transfusion volume and incidence

Cardiac surgery

Transfusion volume

A meta-analysis of six trials reported no significant difference in blood transfusion volume.[178](#_ENREF_178)

Faraoni et al (2012)[179](#_ENREF_179) conducted several meta-analyses investigating 24-hour postoperative transfusion volume. No difference in transfusion volume was observed when studies with a high risk of bias were excluded.

Schouten et al (2009)[181](#_ENREF_181) reported a significant difference in RBC transfusion volume favouring aprotinin.

Ferreira et al (2010)[188](#_ENREF_188) reported no significant difference in intraoperative RBC transfusion volume.

Flaujac et al (2007)[189](#_ENREF_189) reported a significant difference in 24-hour postoperative transfusion volume favouring aprotinin (18 ml/kg versus 30 ml/kg, p=0.01).

Sarupria et al (2013)[190](#_ENREF_190) reported a significant difference favouring high dose EACA over placebo for intraoperative transfusion volume of RBCs and FFP and total transfusion volume of RBCs and FFP.

Singh et al (2001)[191](#_ENREF_191) compared two doses of aprotinin in 75 paediatric cyanotic patients with tetralogy of Fallot undergoing total correction with CPB. A significant difference favouring aprotinin was reported for blood transfusion volume (two doses: 1.1 ± 1.1, one dose: 0.91 ± 0.75 versus 2.2 ± 1.0, p<0.05).

Transfusion incidence

A meta-analysis (including several sensitivity and subgroup analyses) of 404 paediatric patients with congenital heart disease undergoing open heart surgery with CPB was conducted.[178](#_ENREF_178) An analysis of good-quality studies and studies with an objective transfusion protocol found significant differences favouring the use of aprotinin.

An assessment of postoperative transfusion volume and incidence in 20 infants undergoing primary corrective cardiac surgery with CPB reported no significant difference for 24-hour postoperative transfusion incidence of RBCs (60% versus 100%, p=0.06).[189](#_ENREF_189)

An assessment of 120 paediatric patients with tetralogy of Fallot undergoing corrective surgery found that EACA reduced the incidence of RBC transfusion (75.0% versus 97.3%, p=0.01).[190](#_ENREF_190)

Scoliosis surgery

Transfusion volume

A meta-analysis of five trials with 207 paediatric patients reported a significant reduction of volume of blood transfused following the administration antifibrinolytics (aprotinin, TXA or EACA).[183](#_ENREF_183) Subanalyses of the different antifibrinolytic agents found that all reduced transfusion volume: aprotinin (p=0.0015), TXA (p=0.0081) and EACA (p=0.042).

One additional RCT provided evidence for transfusion volume.[193](#_ENREF_193) It reported a significant difference in autologous blood units transfused, favouring EACA (p=0.002).

Transfusion incidence

A meta-analysis of four trials with 163 patients found no significant difference in transfusion incidence (p=0.28).[198-201](#_ENREF_198) No significant difference in transfusion incidence for the different antifibrinolytic agents was found in subanalyses. For allogeneic transfusion incidence, there was a significant difference favouring aprotinin, but not TXA or EACA.

In paediatric patients aged 11–18 years with idiopathic scoliosis who were scheduled for posterior spinal fusion, there was no difference in allogeneic transfusion incidence (no events in either group).[193](#_ENREF_193)

Craniofacial surgery

One systematic review[182](#_ENREF_182) included data from two Level II studies[202-203](#_ENREF_202) and one Level III study.[204](#_ENREF_204) An additional two Level II studies were identified.[195-196](#_ENREF_195)

Transfusion volume

A study of 138 children undergoing craniosynostosis surgery included a meta-analysis to assess RBC transfusion volume, and found a significant difference favouring TXA (p=0.0004).[182](#_ENREF_182)

Two additional Level II studies provided evidence for transfusion volume.[182](#_ENREF_182) One study reported significant differences for total intraoperative RBC transfusion volume (380 ± 90 versus 550 ± 200, p=0.004) and intraoperative RBC transfusion volume by weight (40 ± 10 versus 60 ± 20, p=0.05), favouring aprotinin.[195](#_ENREF_195) The other study reported significant differences in intraoperative blood transfusion volume (32 ± 25 versus 52 ± 34, p=0.04) and postoperative RBC transfusion volume (33 ± 24 versus 57 ± 38, p=0.03) which favoured aprotinin.[196](#_ENREF_196)

An updated meta-analysis was performed. A significant reduction in RBC transfusion volume was demonstrated.

Transfusion incidence

One study assessed transfusion incidence in 26 paediatric patients undergoing major reconstructive craniofacial surgery.[195](#_ENREF_195) No difference in postoperative RBC was demonstrated.

One study in the USA assessed transfusion incidence in 39 paediatric patients aged 1 month to 12 years who were undergoing craniofacial reconstruction.[196](#_ENREF_196) No significant difference was observed.

ENT surgery

One Level I study[180](#_ENREF_180) that included evidence from one Level II study[205](#_ENREF_205) provided evidence for transfusion volume or incidence in paediatric patients undergoing ENT surgery.

Transfusion incidence

One study of 400 children undergoing primary isolated adenoidectomy found no significant difference in transfusion incidence between the topical TXA and placebo groups.[205](#_ENREF_205)

##### Thromboembolic events

One Level I study,[183](#_ENREF_183) which included one Level II study[206](#_ENREF_206) and three Level II studies,[189](#_ENREF_189); [193](#_ENREF_193); [195](#_ENREF_195) provided evidence for thromboembolic events.

One study assessed thromboembolic events in paediatric patients undergoing cardiac surgery.[189](#_ENREF_189) It included 20 infants undergoing primary corrective cardiac surgery with CPB. No thrombotic events were reported in either study group.

Two studies assessed paediatric patients undergoing scoliosis surgery.[193](#_ENREF_193); [206](#_ENREF_206) In one study, no deep venous thrombosis (DVT) occurred in the aprotinin group (0%) compared with three DVTs in the placebo group (13%).[206](#_ENREF_206) This result was not significant (p=0.21). The other study reported no events of venous thrombosis or thromboemboli during the study period.[193](#_ENREF_193)

One study measured thrombotic complications in 26 paediatric patients undergoing major reconstructive craniofacial surgery.[195](#_ENREF_195) No events were reported.

##### Bleeding events

Cardiac surgery

Two Level I studies provided evidence for blood loss in paediatric patients undergoing cardiac surgery.[178-179](#_ENREF_178)

No significant difference in postoperative chest tube drainage was reported in a meta-analysis of 11 trials that included 571 paediatric patients with congenital heart disease undergoing open heart surgery with CPB.[178](#_ENREF_178)

A meta-analysis of trials of 848 paediatric patients reporting 24-hour postoperative blood loss found no significant difference between the TXA and placebo groups (p=0.11).[207](#_ENREF_207) Two sensitivity analyses were also conducted; the first excluded a study by Chauhan et al (2004a)[208](#_ENREF_208) and the second excluded all studies by Chauhan and colleagues. This was to reduce possible bias introduced by these authors, whose studies dominated the original meta-analysis. Two sensitivity analyses (one of which included seven trials and the other five trials) favoured TXA. A subgroup analysis of acyanotic patients showed no significant difference (p=0.47).[207](#_ENREF_207)

Five additional Level II studies provided evidence for postoperative blood loss.

One study assessed blood loss in 80 children with tetralogy of Fallot undergoing intracardiac repair.[186](#_ENREF_186) It found a significant difference in 24-hour postoperative blood loss favouring TXA (p<0.01). In the TXA group, there were two cases (5.0%) of excessive bleeding (>5 mL/kg) due to hyperfibrinolysis, compared to five cases (12.5%) in the control group. This result was not significant.

A study measuring 48-hour postoperative bleeding in 19 paediatric patients with congenital heart disease undergoing cardiac surgery with CPB found no significant difference.[188](#_ENREF_188)

Blood loss was assessed in 120 paediatric patients undergoing cardiac surgery with CPB for tetralogy of Fallot in a three-arm study of high-dose EACA, low-dose EACA and placebo.[190](#_ENREF_190) When high-dose and low-dose EACA were compared, significant differences were found in favour of low-dose EACA for 6-hour postoperative blood loss (108.45 ± 61.45 versus 32.75 ± 26.02, p<0.01), cumulative 12-hour postoperative blood loss (172.37 ± 71.56 versus 50.50 ± 42.30, p<0.01) and cumulative 24-hour postoperative blood loss (223.95 ± 83.96 versus 69.00 ± 50.01, p<0.01). However, when high-dose EACA was compared to placebo, only 6-hour postoperative blood loss reached significance in favour of EACA (108.45 ± 61.45 versus 137.84 versus 52.50, p<0.05). No significant difference was found in cumulative 12-hour or 24-hour postoperative blood loss.

One study assessed total blood loss and 24-hour chest tube drainage among 75 paediatric cyanotic patients with tetralogy of Fallot undergoing total correction with CPB using either one or two doses of aprotinin.[191](#_ENREF_191) There was a significant difference in total blood loss (two doses: 221.4 ± 60.3, one dose: 254.2 ± 22.6 versus 426.0 ± 92.0; p<0.05) and 24-hour chest tube drainage (two doses: 164.3 ± 25.7, one dose: 145.2 ± 20.5 versus 321.0 ± 23.0, p<0.05), favouring aprotinin.

Blood loss was measured in 62 paediatric patients with cyanotic congenital heart disease and a right-to-left shunt undergoing open heart surgery.[192](#_ENREF_192) There was no significant difference in total postoperative blood loss (195.63 ± 188.03 versus 186.30 ± 163.78, p=0.5) or postoperative blood loss by weight (12.51 ± 13.20 versus 10.68 ± 6.38, p=0.5).

Scoliosis surgery

A meta-analysis of five trials that enrolled 163 paediatric patients undergoing scoliosis surgery found a significant difference for total blood loss, favouring antifibrinolytics (aprotinin, TXA or EACA) (p<0.00001).[183](#_ENREF_183)

One study[194](#_ENREF_194) assessed 125 patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis in a three-armed RCT. When TXA or EACA were compared to placebo, there was no significant difference in drain volume. However, there were significant differences in total blood loss (1663.0 ± 882 versus 2116.0 ± 1202, p=0.019) and intraoperative estimated blood loss (776 versus 1080, p=0.019), favouring TXA or EACA. That study also compared TXA with placebo and EACA with placebo.[194](#_ENREF_194) For TXA, there was no significant difference in intraoperative estimated blood loss, but significant differences were observed for total blood loss (1531 ± 911 versus 2116 ± 1201, p=0.015), drain volume (789 ± 449 versus 1034 ± 559, p=0.027) and intraoperative estimated blood loss with mean arterial pressure <75 mmHg (715 versus 1124, p=0.042), all favouring TXA. For EACA, the only significant difference was in intraoperative estimated blood loss (769 ± 1080, p=0.037), favouring EACA. No significant differences were observed for total blood loss, drain volume or intraoperative estimated blood loss with mean arterial pressure <75 mmHg.

Craniofacial surgery

One poor-quality Level I study[182](#_ENREF_182) that included two Level II studies and two Level III studies, plus an additional two Level II studies [195-196](#_ENREF_195) were identified.

A meta-analysis of 138 children undergoing craniosynostosis surgery to assess perioperative blood loss found a significant difference favouring TXA (p=0.0006).[182](#_ENREF_182)

Drain output (ml) at various times following surgery was measured in 26 paediatric patients undergoing major reconstructive craniofacial surgery.[195](#_ENREF_195) No significant differences were reported.

Since Level III evidence did not meet the inclusion criteria for this overview, we performed our own meta-analysis of Level II studies, which excluded the Level III studies included in the Level I study.[182](#_ENREF_182) This analysis demonstrated a significant reduction in postoperative blood loss (p<0.0001).

ENT surgery

This review identified one Level I study[180](#_ENREF_180) that included one Level II study[205](#_ENREF_205) and two Level II studies[197](#_ENREF_197); [209](#_ENREF_209) for ENT surgery.

A study of 400 children undergoing primary isolated adenoidectomy found a significant difference in blood loss, favouring topical TXA.[205](#_ENREF_205)

In an assessment of blood loss in 95 children scheduled for adenotonsillectomy, an intention-to-treat analysis of total intraoperative bleeding showed no difference between groups.[209](#_ENREF_209)

An assessment of surgical field ratings among children with chronic rhinosinusitis undergoing endoscopic sinus surgery found a reduction in moderate bleeding (surgical field rating grade 3) favouring TXA at 15 minutes (16.0% versus 48.0%, p=0.0006) and 30 minutes after beginning surgery (4.0% versus 42.0%, p<0.0001).[197](#_ENREF_197) There was also a significant difference in bleeding volume, favouring TXA (102 ± 19 versus 153 ± 23, p<0.0001).

Clinical commentary – antifibrinolytics in neonatal and paediatric patients undergoing surgery

The effect of antifibrinolytics on mortality in neonatal and paediatric patients is unknown. The included studies found no difference in mortality but were underpowered. Effects on transfusion volume were as follows:

* In paediatric cardiac surgery, the use of antifibrinolytics reduced transfusion volume. The strong evidence in the adult cardiac surgery population provides additional support to the recommendation that paediatric patients undergoing cardiac surgery should receive TXA.
* In scoliosis surgery, antifibrinolytics reduce transfusion volume. The reduction was clinically significant, and was similar for aprotinin, TXA and EACA.
* In craniofacial surgery, aprotinin and TXA reduce transfusion volume.
* In ENT surgery, topical TXA did not reduce transfusion incidence.

There are dose-dependent safety concerns for the use of antifibrinolytic drugs in adults; these include increased mortality, renal dysfunction, thrombosis, seizures and hypersensitivity. It is uncertain whether these concerns extend to the paediatric population. Neonates and those with central venous access devices in place may be at increased risk of thrombosis. However, the studies included in this review were underpowered to determine the risk of these adverse events.

A large retrospective cohort study in children undergoing congenital heart surgery did not find any difference in mortality or need for dialysis in children receiving aprotinin compared to those not receiving aprotinin.[210](#_ENREF_210)

Antifibrinolytics should be used at a dose that results in the greatest reduction of blood loss with the fewest side effects. The regimes of antifibrinolytics in this systematic review varied markedly between studies in dose, timing of boluses and use of infusions. There is little information on pharmacokinetics and pharmacodynamics of aprotinin in paediatrics. Data on TXA pharmacokinetics and dose required to inhibit hyperfibrinolysis in paediatrics are now emerging in craniofacial and cardiac surgery.[211-212](#_ENREF_211) Future dose regimens will probably be based on age and weight.

### 3.5.9 Neonatal and paediatric patients undergoing surgery – effects of rFVIIa on outcomes

| Evidence statements – surgical (rFVIIa) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.34 | In infants aged <1 year requiring cardiac surgery with CPB, the effect of prophylactic rFVIIa compared with no rFVIIa on mortality is uncertain.  (See evidence matrix D4.V in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√√ |
| ES4.35 | In paediatric patients aged >1 year undergoing cardiac surgery, the effect of rFVIIa compared with no rFVIIa on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.36 | In infants aged <1 year requiring cardiac surgery with CPB, the effect of prophylactic rFVIIa compared with no rFVIIa on transfusion incidence is uncertain.  (See evidence matrix D4.W in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√√ |
| ES4.37 | In paediatric patients aged >1 year undergoing cardiac surgery, the effect of rFVIIa compared with no rFVIIa on transfusion volume and incidence is unknown. | NA | NA | NA | NA | NA |
| ES4.38 | In infants aged <1 year requiring cardiac surgery with CPB, the effect of prophylactic rFVIIa compared with no rFVIIa on thromboembolic events is uncertain.  (See evidence matrix D4.X in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √√√ |
| ES4.39 | In paediatric patients aged >1 year undergoing cardiac surgery, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES4.40 | In paediatric patients undergoing cardiac surgery, the effect of rFVIIa compared with no rFVIIa on bleeding events is unknown. | NA | NA | NA | NA | NA |
| CPB, cardiopulmonary bypass; ES, evidence statement; rFVIIa, recombinant activated factor VII  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – surgical (rFVIIa) | |
| R12  (Grade C) | In paediatric patients undergoing cardiac surgery with CPB, the *routine* use of rFVIIa is not recommended. |
| Practice point – surgical (rFVIIa) | |
| PP39 | 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  a rFVIIa is not licensed for this use; its use should only be considered in exceptional circumstances.  b See R22 and PP20 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) |
| CPB, cardiopulmonary bypass; PP, practice point, R, recommendation; rFVIIa, recombinant activated factor VII | |

#### Background

rFVIIa activates the formation of prothrombinase complex. It has a local mode of action in areas where tissue factor or phospholipid are exposed. At pharmacological doses, rFVIIa bypasses conventional steps in the coagulation cascade and acts directly on activated platelets at the injury site, leading to the generation of a fully stabilised fibrin clot.

#### Summary of evidence

One good-quality systematic review[213](#_ENREF_213) that included one RCT[214](#_ENREF_214) was identified. Patients in the RCT were infants under 1 year of age with congenital heart disease who required surgery with CPB.

##### Mortality

No deaths were reported in the included study.

##### Transfusion volume and incidence

The study reported no difference in transfusion incidence.[214](#_ENREF_214) Transfusion volume was not reported.

##### Thromboembolic events

No thromboembolic events were reported in the included studies.

##### Bleeding events

No bleeding events were reported in the included studies.

Clinical commentary – rFVIIa in neonatal and paediatric patients undergoing surgery

There is limited evidence regarding the use of rFVIIa in paediatric patients. There are concerns about safety, particularly about thromboembolic events. Its routine use is not advised; however, it may have a role in patients with life-threatening haemorrhage, where conventional measures have been ineffective. In Australia, rFVIIa is not licensed for use in major bleeding, and its role should be limited to exceptional circumstances.

### 3.5.10 Neonatal and paediatric patients undergoing surgery – effects of miniaturised CPB systems on outcomes

| Evidence statements – surgical (miniaturised CPB systems) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.41 | In infants aged <1 year undergoing cardiac surgery with CPB and extracorporeal circulation support, the effect of a miniaturised CPB system compared with a standard-sized system on mortality is uncertain.  (See evidence matrix D4.Y in Volume 2 of the technical report.) | X | NA | NA | √√√ | √ |
| ES4.42 | In paediatric patients aged >1 year undergoing cardiac surgery with CPB, the effect of a miniaturised CPB system compared with a standard-sized system on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.43 | In infants aged <1 year undergoing cardiac surgery with CPB and extracorporeal circulation support, the effect of a miniaturised CPB system compared with a standard-sized system on transfusion volume is uncertain.  (See evidence matrix D4.Z in Volume 2 of the technical report.) | X | NA | √ | √√√ | √ |
| ES4.44 | In infants aged <1 year undergoing cardiac surgery with CPB and extracorporeal circulation support, the effect of a miniaturised CPB system compared with a standard-sized system on transfusion incidence is unknown. | NA | NA | NA | NA | NA |
| ES4.45 | In paediatric patients aged >1 year undergoing cardiac surgery with CPB, the effect of a miniaturised CPB system compared with a standard-sized system on transfusion volume and incidence is unknown. | NA | NA | NA | NA | NA |
| CPB, cardiopulmonary bypass; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Background

Miniaturised CPB systems may reduce the systemic inflammatory response, haemodilution and coagulopathy often seen with standard-sized CPB systems. In paediatric patients undergoing surgery this may lead to reduced transfusion volume or incidence and risk of mortality.

#### Summary of evidence

One poor-quality RCT involving 60 paediatric patients under 1 year of age scheduled for cardiac surgery with CPB was identified.[215](#_ENREF_215)

##### Mortality

No deaths were reported in the included study.

##### Transfusion volume and incidence

The study reported no significant difference in the volume of RBCs transfused.[215](#_ENREF_215)

### 3.5.11 Critically ill neonatal and paediatric patients – effects of rFVIIa on outcomes

| Evidence statements – critically ill (rFVIIa) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.46 | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.47 | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES4.48 | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
| ES4.49 | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; rFVIIa, recombinant activated factor VII  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Background

rFVIIa activates the formation of prothrombinase complex. It has a local mode of action in areas where tissue factor or phospholipid are exposed. At pharmacological doses, rFVIIa bypasses conventional steps in the coagulation cascade and acts directly on activated platelets at the injury site, leading to the generation of a fully stabilised fibrin clot.

#### Summary of evidence

This review did not identify any eligible Level I or Level II studies.

Clinical commentary – rFVIIa in critically ill paediatric patients

There is limited evidence regarding the use of rFVIIa in paediatric patients. There are concerns about safety, particularly about thromboembolic events. Its routine use is not advised; however, it may have a role in patients with life-threatening haemorrhage, including trauma patients and those on extracorporeal life support (ECLS), where conventional measures have been ineffective. In Australia, rFVIIa is not licensed for use in major bleeding, and its role should be limited to exceptional circumstances.

### 3.5.12 Critically ill neonatal and paediatric patients – effects of viscoelastometric POC testing on outcomes

| Evidence statements – critically ill (viscoelastometric POC testing) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
| ES4.50 | In critically ill paediatric patients, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on mortality is unknown. | NA | NA | NA | NA | NA |
| ES4.51 | In critically ill paediatric patients, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
| ES4.52 | In critically ill paediatric patients, the effect of viscoelastometric POC testing compared with no viscoelastometric POC testing on bleeding events is unknown. | NA | NA | NA | NA | NA |
| ES, evidence statement; POC, point of care  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

#### Background

Viscoelastometric POC testing includes TEG and ROTEM. These tests measure clot development, stabilisation and dissolution (fibrinolysis), which reflect in vivo haemostasis. In critically ill paediatric patients, these techniques offer improvements over traditional laboratory testing in the assessment of bleeding patients.

#### Summary of evidence

This review did not identify any eligible Level I or Level II studies.

Clinical commentary – viscoelastometric POC testing in critically ill paediatric patients

Further studies are required to clarify the role of viscoelastometric POC testing in neonatal and paediatric critical care patients, including those undergoing ECLS.

## 3.6 Considerations for Aboriginal and Torres Strait Islander neonates and children

### 3.6.1 Key points

As recipients of health care, Aboriginal and Torres Strait Islander (referred to hereafter as Indigenous) neonates and children are entitled to culturally safe health care.[[14]](#footnote-14) Also, the distance between the neonate’s or child’s residence and the health-care service should be considered. These aspects apply to this and the previous five modules in these guidelines.

All the recommendations, practice points and expert opinion points identified in this module apply to Indigenous neonates and children. Additional information is given here to highlight the effect of social determinants in relation to anaemia in Indigenous children.

Indigenous women and babies in Australia continue to have poor maternal and infant outcomes.[217](#_ENREF_217) Maternal factors affect the child’s risk of iron deficiency and anaemia. These factors include:

* higher fertility rate (2.6% Indigenous versus 1.9% non-Indigenous in 2009)[226](#_ENREF_226) and higher parity
* more frequent teenage births (21% Indigenous versus 4% non-Indigenous in 2009)[226](#_ENREF_226)
* more limited access to affordable nutritious food[226](#_ENREF_226)
* higher rates of medical comorbidities, such as chronic renal disease, diabetes, chronic vascular disease and rheumatic heart disease[226](#_ENREF_226)
* higher rates of hookworm in certain communities[227](#_ENREF_227)
* higher rates of *Helicobacter pylori*.[228](#_ENREF_228)

Other factors that disproportionately affect Indigenous Australians include:

* more likely to live in remote communities[226](#_ENREF_226); [229](#_ENREF_229)
* less likely to participate in preventative health care[226](#_ENREF_226)
* less engagement in antenatal care (due to a variety of factors including lack of culturally safe services, financial barriers, transport issues and other community or family commitments that take priority)[229](#_ENREF_229)
* more frequent single-parent families[226](#_ENREF_226)
* higher smoking rate.[226](#_ENREF_226); [229](#_ENREF_229)

These factors may contribute to the higher frequency of low birth weight and preterm birth than in non-Indigenous women (13.8% versus 8.1%).[226](#_ENREF_226); [229](#_ENREF_229)

There is a high prevalence of IDA in children from remote Indigenous communities.[28](#_ENREF_28) A retrospective cohort study of 398 Indigenous infants from remote northern Australia found that 68% of children were anaemic.[27](#_ENREF_27) Also, the Early Childhood Nutrition and Anaemia Prevention Project found that nearly 90% of infants and young children were anaemic at least once between 6 months and 2 years of age.[26](#_ENREF_26)

Risk factors for Indigenous children to develop iron deficiency include maternal iron deficiency, low birth weight, late or insufficient introduction of iron-rich solids and a higher burden of infectious disease such as hookworm infection.[28](#_ENREF_28); [30](#_ENREF_30); [230](#_ENREF_230) Babies born to Indigenous women are twice as likely to be of low birth weight, which is a risk factor for iron deficiency and anaemia.

Maternal nutritional status exerts a significant influence on fetal iron status, emphasising the importance of maternal iron sufficiency in reducing the risk of anaemia in the child.[231](#_ENREF_231) Indigenous women who live in remote areas were significantly more likely to have low Hb levels than those in non-remote areas (10.1% compared with 6.9%).[230](#_ENREF_230) Because Indigenous babies are considered to be at a higher risk of IDA, deferred cord clamping should be considered (see Section 3.5.1).

A number of gaps in the evidence have been identified in this module, and an overriding consideration is the paucity of studies that specifically identify Indigenous neonates and children among the participants.

The Congress of Aboriginal and Torres Strait Islander Nurses and Midwives (CATSINaM), the Australian College of Midwives and CRANA Plus[[15]](#footnote-15) provide the following points:[[16]](#footnote-16)

* Care should be person-centred, with Australian Indigenous neonates, children and their families acknowledged as individuals with needs, values and preferences that must be considered within health-care decisions that are considered nonurgent.
* Care should be honest, with transparency of information and options around standard practices at the time of birthing (e.g. deferred cord clamping or collection of cord blood), so that Australian Indigenous women (and parents) can make informed choices that suit their infants and children.
* Care should be respectful, with choice and flexibility for Australian Indigenous parents and legal guardians, and parents and guardians should be supported within those choices (e.g. through initiatives to increase safety away from health services, and to increase cultural aspects within services)*.*
* Care should be provided with cultural integrity and safety, and coordinated according to the needs of the Australian Indigenous neonate and child; these should include cultural, emotional and psychosocial needs, as well as clinical needs.
* Care should be collaborative and multidisciplinary, with health professionals respectfully placing Australian Indigenous parents, legal guardians and families at the centre of the service being provided.

# 4 Background questions

The CRG developed background questions in relation to PBM for neonatal and paediatric patients. Key issues in relation to neonatal and paediatric patients are:

their changing body composition and physiology related to development and growth, which means that the risks and benefits for this population can differ from those that apply to adult patients

the potential for lifelong consequences of treatments given during infancy and childhood

certain disorders that are unique to infancy and childhood.

Background questions 1 and 3 address the special vulnerability of young patients. The first question addresses the circumstances in which the use of blood products that have been selected on the basis of specific characteristics or that have been specially treated may improve short or long-term outcomes. The third question relates to the fact that blood loss due to phlebotomy and sampling lines can substantially contribute to the risk of anaemia and incidence of transfusion in neonatal and paediatric patients who undergo prolonged hospitalisation, have high severity of illness or have chronic conditions. The question explores methods to miminise these losses.

Background question 2 addresses fetal transfusion, which was the earliest form of fetal treatment and remains among the most successful.

Background questions 4 and 6 cover issues that have been addressed as general or specific questions for other modules, but in which there are substantial differences between adults and children that lead to uncertainties about whether adult evidence can be extrapolated. Because there are low levels of evidence in relation to children, these questions have been readdressed in this module as background questions. The main issues are the use of haemostatic agents to prevent excessive blood loss in neonatal and paediatric patients undergoing major surgery (Background question 4), and the need to adapt the massive transfusion protocol developed in Module 1 (*Critical Bleeding/Massive Transfusion*[1](#_ENREF_1)) for neonatal and paediatric patients (Background question 6). The massive transfusion protocol has been renamed here as a ‘critical bleeding protocol’ to more accurately reflect the clinical problem, rather than just one of the modalities used to address it.

Infants and children have particular risk factors for IDA. Background question 5 explores these risk factors and provides guidance about iron therapy.

## 4.1 Selection of blood products

Background question 1

For fetal, neonatal or paediatric patients, does selection of specific blood products, when compared with routine blood products, improve outcomes?

### 4.1.1 Use of ‘fresh’ RBCs in fetal, neonatal or paediatric patients

For fetal, neonatal or paediatric patients, do ‘fresh’ (≤7 days) RBCs, when compared with older RBCs, improve outcomes?

RBC, red blood cells

Retrospective and prospective studies have raised concerns that patients receiving older blood have an increased mortality compared to patients receiving newer stored units.

Refrigerated storage results in a ‘storage lesion’, characterised by metabolic derangements, changes in RBC shape and rheology, loss of membrane carbohydrates, oxidative injury to lipids and proteins, changes in oxygen affinity and delivery, increased adhesion of RBCs to endothelial cells, and reduced lifespan.[232](#_ENREF_232) There are also secondary risks of rising concentrations of potassium and plasticiser, and shedding of active proteins, lipids and microvesicles.[232](#_ENREF_232) Together, these storage-related changes could increase the risks and reduce benefits of transfusion, but it is not clear whether they have a significant effect on clinical outcomes.[233](#_ENREF_233) The circumstances in which guidelines have suggested use of fresher RBCs are those in which:

toxic effects may be magnified by the patient’s immaturity or by the size, rapidity or frequency of transfusion

even small increases in the longevity of the transfused RBCs may be a major advantage.

There is insufficient evidence on which to base strong recommendations for the use of ‘fresh’ RBCs in fetal, neonatal or paediatric patients. Nevertheless, the circumstances in which ‘fresh’ RBCs are recommended in previous guidelines include:

fetal intrauterine transfusion (IUT)[234-236](#_ENREF_234)

exchange transfusion and large-volume (e.g. >25 mL/kg) transfusion of neonates and infants under 1 year of age[237-239](#_ENREF_237)

infants and children undergoing cardiac surgery using CPB

chronically transfused patients.[240](#_ENREF_240)

For infants and children undergoing cardiac surgery using CPB, a retrospective study reported lower rates of major complications in those in whom ‘fresh blood’ (<4 days old) was used to prime the CPB circuit.[241](#_ENREF_241)

For neonatal patients undergoing top-up transfusion, a randomised trial found no difference in mortality or acute organ dysfunction between infants receiving RBCs stored for <7 days (mean 5.1 days) and those receiving older RBCs (mean 14.6 days).[242](#_ENREF_242) In contrast, in observational studies, transfusion of older RBCs in PICU patients has been associated with increased incidence of multiorgan failure and PICU length of stay.[243-244](#_ENREF_243)

In the chronically transfused patient, it is desirable to maximise the RBC in vivo survival time. It is thought that by transfusing fresher RBCs, the RBC will last for longer, potentially extending the transfusion interval.[241-242](#_ENREF_241); [245](#_ENREF_245)

|  |  |
| --- | --- |
| Expert opinion point – ‘fresh’ RBCs in fetal, neonatal and paediatric patients | |
| EOP5 | The routine use of ‘fresh’ (<7 days) RBCs is not advocated for routine use, but may be considered in the following clinical situations:  IUT (<5 days, if available)  large-volume transfusion (>25 mL/kg)  exchange transfusion  cardiac surgery  transfusion-dependent chronic anaemia (RBCs <14 days)  where irradiated blood products are used. |
| EOP, expert opinion point; IUT, intrauterine transfusion; RBC, red blood cell | |

### 4.1.2 Kell antigen system

Antibodies against Kell blood group antigens can cause severe transfusion reactions and HDFN. Anti-K antibodies develop as a result of blood transfusion (50–88% of sensitisations), or through pregnancy.[246-247](#_ENREF_246)

Avoiding transfusion-related Kell sensitisation of women and girls who may bear children is an important priority. Where possible, K-negative RBCs should be selected for transfusion for all females of childbearing potential who are K negative or whose K antigen status is unknown. In Australia, donor K status is generally indicated on the blood product label.

To reduce the risk of alloimmunisation and transfusion reactions, both male and female chronically transfused patients (e.g. patients with haemoglobinopathies or congenital anaemia) should have an extended phenotype performed before their first RBC transfusion. Transfusions should be routinely matched for K and also Rh (D, C, c, E, e) antigens.[240](#_ENREF_240); [247](#_ENREF_247)

|  |  |
| --- | --- |
| Expert opinion points – Kell antigen system | |
| EOP6 | Where possible, K-negative RBC should be selected for transfusion for all females of childbearing potential who are K negative or whose K antigen status is unknown. This includes fetal transfusion. |
| EOP7 | In both male and female chronically transfused patients, RBC should be selected to match RhD, RhC/c, RhE/e and Kell antigen status. |
| EOP, expert opinion point; K, Kell; RBC, red blood cell | |

### 4.1.3 Use of irradiated cellular blood products in neonates and children

TAGVHD is a rare and usually fatal complication of transfusion of cellular blood products. It is caused by failure to destroy donor T lymphocytes, which then proliferate and cause an immune response. TAGVHD occurs in immunocompromised recipients; it may also occur in immunocompetent recipients of products from a related or human leucocyte antigen (HLA)-matched donor.

TAGVHD is prevented by using irradiated (with 25 Gy gamma radiation) cellular blood components; leucodepletion alone is insufficient. It is not necessary to irradiate acellular products such as FFP, cryoprecipitate, IVIg, albumin and factor concentrates. Blood stem cells for the purposes of transplantation must not be irradiated.

Table 4.1 Indications for irradiation of cellular products

|  |  |  |
| --- | --- | --- |
|  | Absolute indications  (RBCs, platelets and granulocytes must be irradiated) | Relative indications  (irradiation of cellular products may be considered) |
| Fetus and neonate | * IUT[17](#_ENREF_17) * IUT and subsequent transfusions up to the age of 6 months[17](#_ENREF_17) | * Neonatal exchange transfusion (provided no critical delay in transfusion) * Neonates with a birth weight of ≤1300 g (especially if gestation <28 weeks or birth weight <900 g)[17](#_ENREF_17) |
| Immunodeficiency | * Known or suspected congenital cellular immunodeficiency (e.g. SCID, Wiskott Aldrich syndrome, ataxia telangiectasia and 22q11 deletion syndromes) |  |
| Specific blood products | * HLA-matched cellular products other than stem cells * Blood components donated by first or second-degree relatives |  |
| Stem cell transplantation | * Allogeneic and autologous transplantation | * See relevant guidelines[17-18](#_ENREF_17); [247](#_ENREF_247) for advice on when use of irradiated products can cease |
| Chemotherapy and malignancy[17](#_ENREF_17) | * Hodgkin lymphoma – indefinitely * Treatment with purine analogues – indefinitely * Treatment with Alemtuzumab (anti-CD52) therapy – at least 12 months from last dose * Treatment with ATG – recommendations for duration are not available, consider indefinitely | * All other patients undergoing chemotherapy should be decided on an individual basis, taking into account the intensity of the immunosuppression |

ATG, antithymocyte globulin; HLA, human leucocyte antigen; IUT, intrauterine transfusion; RBC, red blood cell; SCID, severe combined immunodeficiency

#### Circumstances where irradiated cellular blood products are not required.

Irradiated cellular blood products are not required in:

* HIV infection
* humoral immunodeficiency
* patients treated with Rituximab
* patients undergoing solid organ transplantation.

#### Cautions in relation to use of irradiated cellular blood products

Irradiation of RBCs used for large-volume transfusion may increase the risk of hyperkalaemia; therefore, the risk of TAGVHD should be balanced against this risk. To minimise the risk of hyperkalaemia in large-volume transfusion, irradiated RBCs should be as fresh as possible (<7 days old) and should be transfused within 24 hours of irradiation.

|  |  |
| --- | --- |
| Expert opinion points – irradiated cellular blood products | |
| EOP8 | Irradiated cellular blood products (RBCs and platelets) are used to prevent TAGVHD, and are indicated for:  IUT, and recipients of prior IUT up to 6 months of age  suspected or known severe congenital T-cell immunodeficiency (e.g. SCID)  severe acquired T-cell dysfunction, related to either disease or drug therapy (see published guidelines[17-18](#_ENREF_17))  HLA-matched cellular blood products (RBCs, platelets and granulocytes).  They may also be considered for:  neonatal exchange transfusion, provided this does not unduly delay transfusion  very low birth weight neonates, especially extremely preterm (<28 weeks) or extremely low birth weight infants  certain patients undergoing chemotherapy (depending on degree of immunosuppression). |
| EOP9 | Stem cells must not be irradiated. |
| EOP10 | Hyperkalaemia may occur when large volumes of irradiated blood are transfused. In patients at risk, irradiated blood should be as fresh as possible (<7 days) and used within 24 hours of irradiation. |
| EOP11 | Patients at high risk of TAGVHD (such as those with T-cell immunodeficiency) should be given clear written information (e.g. in the form of patient information leaflets or cards). Alerts should be incorporated in the hospital medical record and the blood bank or pharmacy IT system. |
| EOP, expert opinion point; HLA, human leucocyte antigen; IT, information technology; IUT, intrauterine transfusion; RBC, red blood cell; SCID, severe combined immunodeficiency; TAGVHD, transfusion-associated graft-versus-host disease | |

### 4.1.4 Use of CMV-negative blood products

For fetal, neonatal or paediatric patients, does selection of specific blood products (e.g. CMV-negative blood products), when compared with routine blood products, improve outcomes?

CMV, cytomegalovirus

Cytomegalovirus (CMV) is common; it gives rise to chronic, persistent and (for the most part) asymptomatic infection. However, CMV infection can be serious or life-threatening in the fetus or newborn, and in patients with severe T-cell deficiency. CMV can be transmitted by cellular blood products, but the risk of transfusion-transmitted CMV infection has reduced as the use of fresh whole blood has diminished and the use of leucodepleted blood components has become routine.

The risk of CMV transmission through blood products is significantly reduced by either donor screening for CMV or prestorage leucodepletion.[248-250](#_ENREF_248) However, CMV transmission can still occur from CMV-seronegative products due to collection from donors who are in the window period between acquisition of virus and seroconversion (who may have high viral load). Transmission from seropositive leucodepleted products can occur due to failure of the leucodepletion filter.[251-252](#_ENREF_251)

#### Selection of CMV-negative blood products

##### Neonates and intrauterine transfusions

Guidelines for neonates vary widely, and include recommendations both for and against routine use of CMV-seronegative products.[234-235](#_ENREF_234); [253-255](#_ENREF_253) With routine leucodepletion, it is likely that the risk of transmission from cellular blood products is low,[251](#_ENREF_251) whereas maternal breast milk represents a common source of infection.

##### Bone marrow transplant, solid organ transplant, and other haematology and oncology patients

Use of CMV-seronegative screened blood components and leucoreduced blood components are probably equivalent in these populations, and both result in a low rate of transmission.[255-257](#_ENREF_255) The statement from the UK’s Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) notes that CMV-seronegative RBCs and platelets can be replaced with standard prestorage leucodepleted components for all these patient groups, including those who may require a transplant in the future.[255](#_ENREF_255)

The routine use of CMV PCR monitoring in seronegative bone marrow transplant patients (and their donors) allows early detection and treatment of CMV infection (either primary acquired or transfusion related).

##### HIV and immunodeficient patients

The SaBTO statement concludes that prestorage leucodepletion is sufficient to prevent the transmission of CMV in HIV-infected patients. In patients with severe combined immunodeficiency (SCID) who are CMV negative, the use of CMV-negative products should be considered.

##### Granulocyte transfusions

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.[255](#_ENREF_255)

|  |  |
| --- | --- |
| Expert opinion points – CMV-negative cellular products | |
| EOP12 | CMV-negative products may be considered in the following situations:  IUT  preterm neonates (up to 28 days after expected date of delivery)  patients with SCID who are CMV negative  stem cell transplantation where both donor and recipient are known to be CMV negative  granulocyte transfusions for recipients who are CMV seronegative, or whose status is unknown.  CMV-negative products are generally not required in other clinical settings. |
| EOP13 | In urgent situations, if CMV-seronegative blood components are not available, CMV-unscreened leucodepleted components should be used to avoid delays. |
| CMV, cytomegalovirus; EOP, expert opinion point; IUT, intrauterine transfusion; SCID, severe combined immunodeficiency | |

### 4.1.5 Use of human platelet antigen-matched platelets

The human platelet antigens (HPAs) are formed by single nucleotide polymorphisms (SNPs) in the platelet glycoprotein genes. These variant glycoproteins can lead to the formation of anti-HPA antibodies when people are exposed to a glycoprotein that does not occur on their own platelets. These exposures are usually secondary to pregnancy or platelet transfusion.

Numerous HPAs have been reported.[258](#_ENREF_258) In Caucasian populations, the most common alloantibodies are directed against HPA-1a, followed by anti-HPA-5b.[259-260](#_ENREF_259) Other alloantibodies may occur more frequently in non-Caucasian populations.[261](#_ENREF_261)

HPAs have been implicated in fetal and neonatal alloimmune thrombocytopaenia (FNAIT), post-transfusion purpura (PTP) and, rarely, immune-mediated platelet refractoriness.

FNAIT is the leading cause of severe thrombocytopaenia in the fetus and neonate and of intracranial haemorrhage (ICH) in term infants.[262-263](#_ENREF_262) It usually results from maternal alloimmunisation against the paternal platelet antigen, leading to the formation of immunoglobulin G (IgG)-class antibodies that can cross the placenta.

Untreated FNAIT is associated with a high rate of ICH (~ 25%), with most occurring before birth; postnatally, the risk is greatest in the first 8 days.[263](#_ENREF_263) However, thrombocytopaenia can last for several weeks.

Prompt recognition and treatment of FNAIT is vital because of the high risk of ICH.[263-264](#_ENREF_263) Investigation of the parent’s HPA type and compatibility testing should be undertaken in suspected cases.

Optimal thresholds for platelet transfusion are uncertain.[47](#_ENREF_47) Guidelines from the British Committee for Standards in Haematology recommend a platelet threshold of 30 × 109/L in term neonates,[234](#_ENREF_234) and 50 × 109/L in preterm neonates.[264](#_ENREF_264) A higher threshold is considered appropriate if there is active bleeding (50 × 109/L, or 100 × 109/L for intracranial bleeding).

Antigen-negative platelets are likely to be effective in 95% of cases.[152](#_ENREF_152); [263](#_ENREF_263); [265-266](#_ENREF_265) If antigen-negative platelets are unavailable, random donor platelets should be used. Maternal platelets are no longer recommended because there are significant logistical issues that delay transfusion.[263-264](#_ENREF_263); [267](#_ENREF_267)

|  |  |
| --- | --- |
| Expert opinion points – use of HPA-matched platelets | |
| EOP14 | For neonates with known or suspected FNAIT, urgent platelet transfusion should be given if platelets are below 30 × 109/L in a term infant or below 50 × 109/L in a preterm infant, even in the absence of clinically significant bleeding.  If there is active bleeding, a higher threshold should be considered (100 × 109/L for intracranial bleeding, and 50 × 109/L for other sites of bleeding).  For neonates with known or suspected FNAIT, a paediatric haematologist should be consulted. |
| EOP15 | For neonates with known or suspected FNAIT, platelet count response to transfusion should be checked within 12 hours. |
| EOP16 | For infants with known or suspected FNAIT, random donor platelets should be used if antigen-matched platelets are not immediately available. Continued use of random donor platelets is acceptable if antigen-matched platelets cannot be obtained. Because of short survival of random donor platelets, repeated transfusion is likely to be needed. |
| EOP17 | For infants with FNAIT, IVIg may be considered.[20](#_ENREF_20) |
| EOP, expert opinion point; FNAIT, fetal and neonatal alloimmune thrombocytopaenia; HPA, human platelet antigen; IVIg, intravenous immunoglobulin | |

### 4.1.6 Use of HLA-matched platelets

HLA-matching of platelets should be considered for management of platelet refractoriness. For practical purposes, platelet refractoriness is defined by an absolute platelet increment of less than 10–20 × 109/L, 1 hour post-platelet transfusion, on two consecutive occasions.

Most cases of platelet refractoriness are due to non-immune causes such as splenomegaly, fever, infection, disseminated intravascular coagulation, veno-occlusive disease and graft-versus-host disease. The use of fresh, ABO-compatible, single-donor apheresis platelets (as opposed to a pooled product) may improve platelet increments. In these cases, the usual practice is to continue daily platelet transfusions where prophylaxis is indicated, although it is not known whether this approach provides benefit when compared to withholding transfusion.

In a minority of cases, platelet refractoriness is attributable to immune causes.[268](#_ENREF_268) Since the introduction of leucodepleted platelets, the incidence of alloimmunisation due to immune causes has decreased.[269](#_ENREF_269) Immune platelet refractoriness is most commonly attributable to antibodies to HLAs, and less often to antibodies to HPAs.

Initial investigation of platelet refractoriness should include screening for HLA antibodies. ABO-compatible, apheresis platelets should be used while waiting for the results of HLA antibody screen. Where there are HLA antibodies, HLA-matched platelets should be used. If HLA antibodies are not detected or there is a poor response to HLA-matched platelets and no obvious non-immune cause, testing for HPA antibodies should be undertaken. If HPA antibodies are detected, then HPA-matched platelets should be used.[270](#_ENREF_270)

Current recommendations are for patients with inherited platelet disorders (e.g. Bernard Soulier Syndrome or Glanzmann’s thrombasthenia) to avoid transfusion if possible, to reduce the risk of alloimmunisation. If there is significant bleeding that has not responded to other treatments, then these patients should receive HLA-matched platelets, because of the potential need for repeated platelet transfusions and the consequent increase in risk of alloimmunisation.[271-272](#_ENREF_271) These recommendations may be revised in the future because of the reduction in HLA alloimmunisation due to universal leucodepletion.[152](#_ENREF_152)

|  |  |
| --- | --- |
| Expert opinion points – use of HLA-matched platelets | |
| EOP18 | For platelet refractoriness attributable to non-immune causes such as splenomegaly or infection, fresh, ABO-compatible, single-donor apheresis platelets may improve platelet increment. |
| EOP19 | If the cause of platelet refractoriness is not obvious, investigation should include screening for HLA antibodies. HLA-matched platelets should be used if an HLA antibody is detected.  If the HLA antibody screen is negative or there is a poor response to HLA-matched platelets, screening for HPA antibodies should be undertaken, followed by use of HPA-matched platelets if positive. |
| EOP20 | In patients with inherited platelet disorders such as Bernard Soulier Syndrome and Glanzmann’s thrombasthenia, platelet transfusions should be avoided if possible, to reduce the patient’s risk of alloimmunisation. If platelet transfusion is unavoidable the patient should receive HLA-matched platelets. |
| EOP, expert opinion point; HLA, human leucocyte antigen | |

### 4.1.7 Washed RBCs

Washing of RBCs before transfusion is undertaken to remove substances (antibodies, serum proteins, additive solutions, increased levels of electrolytes, other cellular metabolites or cytokines) that may be harmful to some patients.[253](#_ENREF_253) Washed units contain 10–20% less RBCs than the original units, but are also depleted of 99% of plasma proteins and have reduced amounts of additive solution and extracellular potassium. Other potential benefits include reduced immunomodulatory effects of transfusion.[273-275](#_ENREF_273) In regard to risks, RBCs may be damaged during the process and thus be more susceptible to haemolysis.47

Washing can be done by the blood bank or, for patients undergoing surgery, with a cell saver. In the blood bank, washing is time and resource intensive, adding 1–2 hours to the product preparation time.23 However, the procedure using a cell saver in the operating theatre takes about 20 minutes in skilled hands, assuming that personnel and equipment are available.

In IUT, washed RBCs packed to a Hct of 75–85% can be used to reduce the volume transfused to the fetus.[276](#_ENREF_276) In paediatric patients receiving large-volume transfusion, washed RBCs may have advantages, but these must be weighed against the increased preparation time.[236](#_ENREF_236) In paediatric patients undergoing cardiac surgery, a systematic review that included three small and heterogeneous trials (two using cells washed in the blood bank and one using a cell-saver technique) comparing washed and unwashed RBCs was inconclusive.[75](#_ENREF_75) In chronically transfused patients, washed RBCs may be considered for the management of severe transfusion reactions, including those due to IgA deficiency.[75](#_ENREF_75); [277-279](#_ENREF_277)

For most small-volume transfusions, the risk of hyperkalaemia is extremely low,[280](#_ENREF_280) and the safety of additive solutions used for RBCs is established.[236](#_ENREF_236) Therefore, routine washing for removal of potassium or additive solution is not necessary.[236](#_ENREF_236)

Overall, there is insufficient evidence to determine whether washed RBCs improve outcomes in fetal, neonatal or paediatric patients.

## 4.2 The need for neonatal transfusion

Background question 2

In fetuses at risk for thrombocytopaenia or anaemia, do particular strategies for detection, intrauterine transfusion and other management improve outcomes and/or reduce the need for neonatal transfusion?

### 4.2.1 Intrauterine fetal blood component transfusion

IUT of RBCs or platelets can reduce perinatal morbidity and mortality associated with severe fetal anaemia or thrombocytopaenia. The most common causes of severe fetal anaemia and thrombocytopaenia that may require IUT are described below, although the use of IUT is not restricted to these aetiologies.

##### Fetal anaemia

HDFN occurs when maternal alloimmunisation against RBC antigens (most commonly RhD, Rhc and Kell) leads to the formation of IgG antibodies that can cross the placenta and cause fetal RBC haemolysis.[169](#_ENREF_169); [281-282](#_ENREF_281) Severe anaemia can also occur as a result of fetal infection with parvovirus B19, and other rarer causes.

Where there is a risk of anaemia due to HDFN or other causes, women should be referred to a maternal fetal medicine specialist for regular ultrasound surveillance that includes Doppler assessment of the middle cerebral artery (MCA) peak systolic velocity (PSV), to monitor for signs of severe fetal anaemia undergoing IUT.[283](#_ENREF_283) In cases of severe fetal anaemia, IUT with RBCs can prevent hydrops and fetal death, and promote prolongation of the pregnancy. Repeat transfusions may be needed, with timing based on empiric time intervals or on MCA PSV values.[284-285](#_ENREF_284)

##### Fetal thrombocytopaenia

IUT of platelets can be used to treat severe fetal thrombocytopaenia due to FNAIT, with the aim of reducing the risk of neonatal ICH. Due to the high risk associated with fetal blood sampling (FBS) and intrauterine platelet transfusion, there has been a move away from platelet IUT and towards non-invasive treatments, especially maternal IVIg. Platelet IUT should be considered in cases of FNAIT where there is recent fetal ICH or a previous history of a severely affected fetus, or in cases refractory to maternal IVIg therapy.[286](#_ENREF_286)

#### Potential complications of IUT

The overall complication rate of 3.1% includes the potential for fetal loss (1.6–1.7% per procedure).[287-288](#_ENREF_287) In HDFN, each IUT can expose the mother to fetal 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.

Table 4.2 Products for IUT

|  |  |
| --- | --- |
| Both RBCs and platelets | |
| * Leucodepleted * CMV negative (although leucodepletion may suffice – see Section 4.1.4) * Irradiated to prevent TAGVHD | |
| RBCs | Platelets |
| * Plasma reduced (Hct 0.75–0.85) * Citrate phosphate dextrose anticoagulant (theoretical risk of toxicity from other additive solutions) * <5 days old * Group O with low-titre haemolysins (or ABO identical with the fetus) * RhD and Kell negative, and RBC antigen negative for maternal alloantibodies * Indirect antiglobulin test cross match compatible with the mother’s plasma | * Compatible with any maternal alloantibody (e.g. anti-HPA) * Hyperconcentrated to 2000–4000 ×109/L |

CMV, cytomegalovirus; Hct, haematocrit; HPA, human platelet antigen; RBC, red blood cell; TAGVHD, transfusion-associated graft-versus-host disease  
Adapted from UK Blood Services (2013)[247](#_ENREF_247)

|  |  |
| --- | --- |
| Expert opinion points – intrauterine fetal blood component transfusion | |
| EOP21 | Management of pregnancies at risk of fetal anaemia or thrombocytopaenia should be undertaken in facilities with appropriate expertise in ultrasound imaging and invasive fetal interventions, and which have access to specific blood products and neonatal intensive care. |
| EOP22 | Pregnancies at risk of fetal anaemia should be assessed by Doppler ultrasound of the fetal MCA PSV, to determine whether FBS and IUT are necessary. |
| EOP23 | Pregnant women who have had a prior pregnancy with fetal or neonatal ICH or thrombocytopaenia due to FNAIT should be managed with IVIg.[20](#_ENREF_20) |
| EOP24 | FBS should be considered to assess response to IVIg in those who have had a previous child with ICH due to FNAIT. |
| EOP, expert opinion point; FBS, fetal blood sampling; FNAIT, fetal and neonatal alloimmune thrombocytopaenia; ICH, intracranial haemorrhage; IUT, intrauterine transfusion; IVIg, intravenous immunoglobulin; MCA, middle cerebral artery; PSV, peak systolic velocity | |

## 4.3 Non-pharmacologic blood conservation strategies

Background question 3

In neonatal and paediatric patients, do non-pharmacologic blood conservation strategies aimed at minimisation of blood loss from sampling reduce the incidence of red cell transfusion?

### 4.3.1 Introduction

Phlebotomy blood loss accounts for most of the total blood loss in children in all age groups during hospitalisation, and is significantly associated with RBC transfusion requirements.[289](#_ENREF_289) Strategies aimed at minimisation of blood loss from sampling should therefore be part of routine blood conservation efforts.

### 4.3.2 Early removal of sampling lines

After adjusting for severity of illness in neonates requiring intensive care, indwelling arterial lines are significantly associated with increased phlebotomy blood loss.[290](#_ENREF_290) In an observational study, overdrawn blood sampling (in excess of laboratory requirements) was higher for central venous lines than indwelling arterial lines, peripheral IV catheters or peripheral draws.[291](#_ENREF_291) However, the safety and efficacy of early removal of sampling lines have not been evaluated in children. A balance of risks associated with indwelling vascular lines, and the difficulty of obtaining samples via other routes should be taken into account.

### 4.3.3 Avoiding excess phlebotomy volumes

Phlebotomy losses can be up to 25% in excess of the need for the analytical procedure in NICU patients, and up to 375% in PICU patients, where the highest losses (in mL/kg) are in the youngest patients.[291-292](#_ENREF_291)

Steps to minimise cumulative phlebotomy volumes include:[293](#_ENREF_293)

adherence to minimum sample volumes needed for analysis

careful sampling, labelling and handling technique, to reduce sample rejection by the laboratory

use of paediatric collection tubes

automated laboratory equipment capable of analysing smaller blood samples

use of non-invasive or POC techniques to estimate Hb, coagulation status, blood gases and other analytes.

Also, see Section 4.3.6.

### 4.3.4 As-needed or rationalisation of blood sampling

There is a strong correlation between severity of critical illness and blood sampling in both NICU and PICU patients.[289](#_ENREF_289); [294](#_ENREF_294) Therefore, in some patients, large phlebotomy losses are an inevitable result of appropriate investigation and monitoring. Nevertheless, strategies that involve rationalisation of laboratory tests have been shown to be safe and effective in adult patients,[295-297](#_ENREF_295) and are widely recommended (although they have not been empirically tested) for chronically or critically ill neonatal and paediatric patients.[298-302](#_ENREF_298)

### 4.3.5 Replacement or avoidance of discard or void volumes in sampling lines

Returning void volumes in sampling lines is traditional practice in many NICUs and PICUs. Passive backflow or active aspiration methods can minimise iatrogenic blood loss and yield reliable analytical results in children.[303](#_ENREF_303) Closed inline blood conservation devices have been demonstrated in adults to be safe and effective in reducing phlebotomy volumes.[304](#_ENREF_304) Thus, they have the potential to reduce RBC transfusion requirements for children, but their cost-effectiveness is untested.[304-305](#_ENREF_304)

### 4.3.6 Non-invasive techniques for testing of Hb, blood gases and other analytes

An inline ex vivo blood gas and chemistry monitoring system (VIA-LVM, VIA Medical, Austin, Texas, USA) attached to an umbilical arterial catheter has been studied in neonates and infants. The system significantly reduced phlebotomy volumes and requirement for transfusion of volume and RBCs in very low birth weight infants.[306-307](#_ENREF_306) Such inline blood analysis devices have become standard in neonatal and paediatric ECLS, but they have not been routinely used in non-ECLS patients. Optimal use of non-invasive techniques such as the respiratory function monitoring capabilities of contemporary ventilators, end-tidal carbon dioxide (ETCO2) monitoring and transcutaneous and regional oxygen saturation (TcSO2, rSO2) monitoring has the potential to reduce phlebotomy losses.

|  |  |
| --- | --- |
| Expert opinion points – strategies for minimisation of blood loss | |
| EOP25 | Strategies to safely minimise phlebotomy losses should be used for all neonatal and paediatric patients. Such strategies may include (where safe and feasible):  use of ‘as-needed’ rather than routine sampling  meticulous avoidance of blood overdraw  return of void volumes to sampling lines  use of closed inline sampling devices  judicious use and ‘on-time’ removal of sampling lines  optimal sampling technique and sample handling to minimise rejection of samples by laboratory  laboratory equipment that uses the smallest possible sample volumes  use of non-invasive techniques and POC devices  audit compliance and cumulative phlebotomy losses in selected groups of patients at regular intervals. |
| EOP, expert opinion point; POC, point of care | |

## 4.4 Strategies to minimise blood loss in cardiac surgery

Background question 4

In perioperative neonatal and paediatric patients undergoing cardiac surgery, do strategies to minimise blood loss reduce the incidence of transfusion?

### 4.4.1 Prothrombin complex concentrate

The prothrombin complex concentrate (PCC) available in Australia[[17]](#footnote-17) contains factors II, IX and X. Because its content of factor VII is clinically insignificant, it is considered a ‘3-factor PCC’.[308-309](#_ENREF_308)

The Australasian Society of Thrombosis and Haemostasis recently updated its advice on reversal of vitamin K antagonist (VKA) in patients with high INR, bleeding and in the perioperative setting.[21](#_ENREF_21) In adults, PCC can quickly and reliably revert the effects of VKA, with the caveat that 3-factor PCC might need to be supplemented with FFP transfusion, as a source of factor VII.[310-311](#_ENREF_310) There are no trials or studies addressing safety and dosing in children; also, 3-factor and 4-factor PCC have not been compared.[312](#_ENREF_312) Nevertheless, PCC may have a role in urgent surgery where there is insufficient time for reversal of VKA using vitamin K. On the basis of observational studies in paediatric[313](#_ENREF_313) and adult[314](#_ENREF_314) patients, low-dose PCC may have a role in controlling bleeding post-CPB.

The use of PCC in lieu of FFP has the potential to reduce the risk of transfusion-associated adverse reactions in neonatal and paediatric patients undergoing surgery.[58](#_ENREF_58); [315-325](#_ENREF_315)

|  |  |
| --- | --- |
| Expert opinion points – strategies for minimisation of blood loss | |
| EOP26 | PCCs may be considered in neonatal and paediatric patients undergoing urgent surgery who are receiving VKAs.[21](#_ENREF_21) |
| EOP27 | PCCs may be considered to treat bleeding in paediatric patients at high risk of volume overload (e.g. those who have undergone cardiac surgery on CPB). |
| CPB, cardiopulmonary bypass; EOP, expert opinion point; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist | |

### 4.4.2 Topical haemostatic agents

Topical haemostatic agents (THAs) can be used in surgery to prevent or control bleeding, as one element of an approach to blood conservation (see Box 4.1).[326-327](#_ENREF_326)

There are a variety of different THAs on the market, with distinct mechanisms of action and characteristics. Some act by compression (pads or cloth-like materials), others by sealing off a bleeding area. They are used mostly for vascular anastomoses, localised oozing spots and at the sternum, when other measures to control haemostasis have failed. In general, THAs decrease the time needed to obtain haemostasis.

Use of these products depends on surgeons’s preference, availability, type of bleeding (arterial or capillary), patient coagulation status (normal or deranged), and tissue or compartment where the product will be used.[328](#_ENREF_328)

The various products have different applications, mechanisms of action and risks.[15](#_ENREF_15); [308](#_ENREF_308); [329-337](#_ENREF_329) Thus, it is critical to follow the manufacturer’s instructions for use, and consider the product-specific safety information.

Box 4.1 Strategies to improve blood conservation in paediatric cardiac surgery[[18]](#footnote-18)

* Careful planning of the surgical procedure, taking blood conservation into account
* Meticulous surgical technique
* Judicious use of diathermy and other electrosurgical technologies
* Systemic antifibrinolytics (e.g. TXA)
* Controlled intraoperative hypotension
* Judicious use of topical agents (e.g. thrombin, collagen and fibrin glue)
* Strategies to facilitate chest re-entry (e.g. closure or reconstitution of the pericardium, and protection of the innominate vein)
* Strategies to decrease mediastinal adhesions (e.g. use of dissolvable suture material where appropriate)
* Consideration of the use of reduced prime volume and smaller circuits for cases operated on under CPB
* Haemofiltration or modified ultrafiltration for cases operated on under CPB[338](#_ENREF_338)
* Cell salvage of residual CPB blood[339](#_ENREF_339)

#### Quality of the evidence

There are few studies of THAs in paediatric patients.[308](#_ENREF_308); [335](#_ENREF_335); [340-356](#_ENREF_340) Recent blood conservation guidelines for adults, from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists in the USA, suggest that the use of THA may be considered based on level C evidence (consensus opinion of experts, case studies or standard of care).[352](#_ENREF_352)

|  |  |
| --- | --- |
| Expert opinion points – THAs | |
| EOP28 | THAs may be considered in neonatal and paediatric surgical patients as an adjuvant to control bleeding. |
| EOP29 | The use of THAs should adhere to the manufacturer’s instructions and safety information. |
| EOP, expert opinion point; THA, topical haemostatic agent | |

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## 4.5 Iron Deficiency Anaemia

Background question 5

In neonates and children, what recommendations should be made for the detection, diagnosis and management of iron deficiency anaemia?

In Australia, the prevalence of anaemia in children under the age of 5 years is about 8%, corresponding to over 100 000 preschool children.[357](#_ENREF_357) Iron deficiency is the largest contributing factor to anaemia in all paediatric age groups.[358](#_ENREF_358)

The prevalence of IDA in children from remote Indigenous communities is high[28](#_ENREF_28) (see Section 3.6). A retrospective cohort study found that 68% of Indigenous infants from remote northern Australia were anaemic.[27](#_ENREF_27) The Early Childhood Nutrition and Anaemia Prevention Project found that nearly 90% of Indigenous infants and young children were anaemic at least once between 6 months and 2 years of age.[26](#_ENREF_26)

Factors that put children at risk of developing IDA include maternal iron deficiency, late or insufficient introduction of iron-rich solids, increased iron requirements, poor intestinal iron absorption and increased loss of iron due to blood loss.

### 4.5.1 Iron requirements in infants and children

#### Term infants

Term infants generally have sufficient iron stores to meet their requirements for the first 4–6 months of life,[359-360](#_ENREF_359) by which time they should be receiving iron-rich solids. Exclusively breast fed term infants require no iron supplementation in the first 6 months of life, provided their mother has sufficient dietary intake. Formula-fed infants should receive an iron-fortified formula.

#### Preterm and low birth weight infants

Neonatal iron stores are largely laid down during the third trimester of pregnancy;[361](#_ENREF_361) therefore, most preterm infants are at risk of subsequent iron deficiency. Iron supplementation should begin in infants born before 32 weeks gestation by 4 weeks of chronological age, once enteral feeds have been established.[362](#_ENREF_362) Preterm infants have a daily requirement of 2–3 mg/kg/day of elemental iron, which can usually be met by iron supplemention until there is adequate dietary iron intake.[104](#_ENREF_104)

Regardless of gestational age, low birth weight infants, particularly those weighing <1800 g, have inadequate iron stores at birth,[104](#_ENREF_104); [362](#_ENREF_362) and should receive iron supplementation until 6 months of age (corrected for gestation at birth).

#### Iron requirements in infants

From 6 months of age, all infants and toddlers should receive iron-rich solids.[359-360](#_ENREF_359) If there is a delay in starting iron-rich solids, low-dose oral iron supplementation (1 mg/kg/day) is recommended until appropriate dietary sources are introduced.[360](#_ENREF_360)

Table 4.3 Iron requirements in neonates and infants

|  |  |  |  |
| --- | --- | --- | --- |
| Age | Iron requirement | Feeding | Supplementation |
| Term; 0–6 months | AI  0.2 mg per day | Breast milk | Not routinely required |
| Iron-fortified formula |
| Term; 6–12 months | RDI  11 mg per day | Breast milk then iron-rich foods | Not routinely required |
| Formula then iron-rich foods |
| Preterm (<32 weeks) or low birth weight infants;  from 1–12 months | 2–3 mg per day provided as either; | Iron-fortified formula with iron-rich foods from appropriate age | 1–2 mg/kg/day of elemental iron until adequate daily iron intake ~6–12 months (corrected for gestation) |
| Breast milk, with iron-rich foods from appropriate age | 2-3 mg/kg/day of elemental iron until adequate daily iron intake ~6–12 months (corrected for gestation) |

AI, adequate intake; RDI, recommended daily intake  
Based on guidelines[104](#_ENREF_104); [360](#_ENREF_360); [363](#_ENREF_363)

#### Children and adolescents

Iron requirements are highest during periods of rapid growth (e.g. in the first 2 years of life and in adolescence). Routine iron supplementation is generally not required in children >1 year of age.

### 4.5.2 Iron deficiency in infants and children

Infants and children with IDA typically present with a subacute or chronic history of progressive pallor, fatigue, irritability, pica, reduced feeding, decreased activity, poor concentration or worsened school performance. Evaluation of a child with iron deficiency should include assessment of possible causes.

### 4.5.3 Diagnosis of IDA

Anaemia is defined as a Hb concentration below the lower limit of the normal reference range, and varies according to age and sex. Laboratory diagnosis of IDA in paediatric patients must take into consideration age-specific reference ranges for full blood count and serum ferritin. It is not appropriate to use adult reference ranges.

Patients with iron deficiency will typically have a reduced mean cell volume (MCV) and mean corpuscular Hb (MCH). A similar hypochromic microcytosis (with or without anaemia) may also be seen in carriers of beta thalassaemia; therefore, microcytosis should not be used in isolation to diagnose iron deficiency.

Serum ferritin is the most useful screening test to assess iron stores; a reduced serum ferritin (<20 µg/L) indicates inadequate iron stores.[364](#_ENREF_364) Serum iron levels are highly variable and should not be used to diagnose iron deficiency.

Serum ferritin is an acute-phase reactant, and a normal result does not exclude iron deficiency in the presence of coexisting infection, inflammation or liver disease. Concurrent assessment of the C-reactive protein can be useful to exclude concurrent inflammation. Serum ferritin levels of <50 µg/L should raise suspicion of iron deficiency in children with chronic disease and in high-risk populations such as Indigenous Australians.[365](#_ENREF_365)

### 4.5.4 Iron therapy in infants, children and adolescents

There is a lack of RCTs on the treatment of IDA in the paediatric population. Trials that are focused on the iron formulation, dose, adverse effects, adherence and total length of therapy are needed to better inform treatment decisions.[366](#_ENREF_366)

RBC transfusion is rarely indicated solely for treatment of IDA, and should be limited to cases with haemodynamic compromise. All patients with IDA, whether or not transfused, should have iron supplementation, to both correct anaemia and replenish body stores.[367-369](#_ENREF_367)

#### Iron supplementation options

##### Dietary therapy

Iron deficiency in infants and toddlers is primarily a nutritional disorder.[360](#_ENREF_360) Hence, measures to improve dietary intake of iron-rich foods are fundamental.[360](#_ENREF_360) Dietary changes alone are usually inadequate to treat IDA.[368](#_ENREF_368)

Standard cow’s milk, goat’s milk and soy milk have a low iron content and should not be offered to infants under 12 months of age.[359](#_ENREF_359) From 12 months of age, cow’s milk intake should not exceed 500 mL per day.[359](#_ENREF_359) In non-breast fed infants in the first 2 years of life, iron-fortified formula can play a role in the prevention and treatment of IDA.[360](#_ENREF_360)

##### Oral iron therapy

Oral iron therapy is safe and effective as first-line therapy in most patients with iron deficiency or IDA.[368](#_ENREF_368)The recommended dose for the treatment of IDA in children is 3–6 mg/kg/day of elemental iron.[360](#_ENREF_360); [368](#_ENREF_368); [370](#_ENREF_370) The dose of iron should take into account the degree of anaemia and weight of the child.

Table 4.4 Quick dose reference to provide 3 mg/kg/day (for severe IDA, consider 6 mg/kg/day)

|  |  |  |  |
| --- | --- | --- | --- |
| Weight (kg) | Ferro-Liquid (30 mg/5 mL) | Fefol ® delayed release capsules ‘spansules’ 87.4 mg | Ferro-Gradumet |
| <10 | 0.5 mL/kg/day | NA | NA |
| 10 – 19 kg | 5 mL per day | Half spansule 5 days/week | NA |
| 20 – 29 kg | 10 mL per day | Whole spansule 5 days/week | NA |
| 30 – 39 kg | 15 mL per day | Whole spansule daily | 1 tablet/day |
| >40 | 20 mL per day | 1.5 spansules daily | 1–2 tablets/day |

Table 4.5 Paediatric appropriate iron formulations in Australia

|  |  |  |  |
| --- | --- | --- | --- |
| Formulation | Name | Elemental iron content | Notes |
| Ferrous sulfate oral liquid | Ferro-Liquid | 6 mg/ml | Maximum daily dose 1 ml/kg |
| Ferrous sulfate delayed release capsules or spansules (270 mg) | Fefol® | 87.4 mg | Spansules can be opened and sprinkled on food to give lower doses  They should not be crushed or chewed |
| Ferrous sulfate (325 mg) | Ferro-Gradumet | 105 mg | May be appropriate and tolerated by the older child or adolescent |

In relation to iron supplementation options, the following considerations apply:

each oral iron preparation contains a different elemental iron dose

over-the-counter multivitamin or mineral supplements should not be used to treat IDA because the iron content is low

compliance and tolerability of iron preparations may be an issue with children:[360](#_ENREF_360)

lower doses or intermittent dosing may be as effective and better tolerated[360](#_ENREF_360); [368](#_ENREF_368)

daily iron dose may be divided into 2–3 doses[360](#_ENREF_360); [371](#_ENREF_371)

oral iron is best absorbed on an empty stomach, ideally 1 hour before or 2 hours after food

consider giving iron preparation with vitamin C (e.g. orange juice) to improve absorption

gastrointestinal upset may be reduced by taking iron with food or at night and increasing the dose gradually

oral iron is best avoided in patients with inflammatory bowel disease due to side effects, poor absorption and exacerbation of inflammation[2](#_ENREF_2)

iron formulations can cause temporary staining of the teeth; brushing teeth with baking soda may ameliorate this

response and compliance should be monitored by measuring Hb and reticulocyte count

oral iron should be continued for 3 months after anaemia has been corrected, to replenish stores.[368-370](#_ENREF_368)

##### Intramuscular iron therapy

Use of intramuscular (IM) iron is discouraged.[367-368](#_ENREF_367)IM iron is effective but painful, may be associated with permanent skin staining and is no safer than IV infusion.[368](#_ENREF_368)

##### IV iron therapy

IV iron should be considered in the following circumstances:[2](#_ENREF_2); [368-369](#_ENREF_368)

* persistent iron deficiency despite oral therapy
* contraindications to oral iron, or serious issues with compliance or tolerance (adverse effects)
* comorbidities affecting absorption (e.g. intestinal mucosal disorders and short gut syndrome) or bone marrow response
* patients receiving ESAs
* ongoing blood loss that exceeds iron absorptive capacity
* requirement for rapid iron repletion (e.g. prevention of physiological decompensation, or preoperatively for non-deferrable surgery)
* genetic disorders of iron transport.

The iron preparations available in Australia are:

* ferric carboxymaltose: [Ferinject®](https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=ferinject&r=http://www.pbs.gov.au/medicine/item/2593L-2805P)
* iron sucrose: [Venofer®](https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=iron%20sucrose&r=http://www.pbs.gov.au/medicine/item/2593L-2805P)
* iron polymaltose: [Ferrosig®](https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=iron%20polymaltose).

ALERT

* Check prescription and vials carefully as there are many different forms of IV iron preparations.
* Iron formulations have different iron concentrations, maximum doses, dilutions and rates of administration and are not interchangeable with regard to dose, dilution and rates of administration.

IV iron should be administered according to a protocol relevant to the specific product used. IV iron sucrose has been shown to be a safe and effective means to treat iron deficiency in children who cannot receive or do not respond to oral iron because of intolerance, poor adherence or iron malabsorption.[372](#_ENREF_372)

A retrospective observational study reported that ferric carboxymaltose was well tolerated and effective in correcting IDA in children aged 0–18 years with inflammatory bowel disease.[373](#_ENREF_373)

The necessary dose of IV iron is calculated based on the patient’s estimated total body iron deficit. Total iron dose per infusion differs among iron products. Hence, the iron dose per infusion should take into account the degree of anaemia, the patient’s weight and the type of IV iron preparation.

Allergic and anaphylactic reactions to IV iron (especially to iron polymaltose) are widely reported.[368-369](#_ENREF_368) Therefore, IV iron should always be administered in an appropriate health-care setting with medical personnel and resuscitation facilities on site. Premedication with steroids and antihistamine may be considered. Drug extravasation has been reported in the paediatric setting as a result of iron infusion, and can cause irreversible skin staining.[374](#_ENREF_374)

Oral iron is not generally required after administration of IV iron if a sufficient dose has been given.

### 4.5.5 Iron toxicity

Iron must be recognised as a potentially lethal medication because it is more toxic than most other prescription medications.[375](#_ENREF_375) Iron overdose in children may be fatal, and iron formulations should be handled and stored appropriately, out of reach of children. In the event of suspected or definite iron ingestion, urgent medical attention should be sought. Information on management of iron toxicity is available.[371](#_ENREF_371)

|  |  |
| --- | --- |
| Expert opinion points – iron therapy | |
| EOP30 | From 6 months of age, all infants and children should receive iron-rich foods. |
| EOP31 | Cow’s milk should not be given to infants before 12 months of age; from 12 months of age, cow’s milk intake should not exceed 500 mL per day. |
| EOP32 | IV iron should be administered according to a protocol relevant to the specific product being used:  IV iron formulations have different iron concentrations, maximum doses, dilutions and rates of administration; they are not interchangeable with regard to dose, dilution and rates of administration  IV iron formulations should only ever be administered in an appropriate health-care setting with medical personnel and resuscitation facilities on site. |
| EOP, expert opinion point; IV, intravenous | |

## 4.6 Critical bleeding

Background question 6

In neonates and children, what recommendations should be made for dealing with critical bleeding?

The definition of critical bleeding is not well established in neonatal and paediatric patients. Also, the evidence about which interventions and strategies result in the best outcomes is limited to case reports, case series, single-centre experience and small retrospective reports.[376-379](#_ENREF_376)

As with adult patients, critical bleeding most commonly occurs in the setting of accidental and non-accidental trauma, major surgeries (particularly cardiac and spinal surgeries, selected neurosurgical procedures and liver transplantation) and gastrointestinal haemorrhage. In neonatal patients, exsanguination due to antepartum or intrapartum fetal haemorrhage, and massive subgaleal haemorrhage are uncommon conditions but are among the indications for large-volume transfusion.

The guideline *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*[1](#_ENREF_1) provides general information and advice. However, on the whole, the evidence is of a low level and is derived from studies on adult populations; thus, it may not be directly applicable to children and neonates.

In the paediatric population, there are age-related physiological variations (particularly in the haemostatic system) that may exacerbate the effects of critical bleeding and large-volume transfusion. These physiological variations are likely to have the greatest impact in neonates, infants and young children.

There is also a marked variation in blood volume with age. It has been suggested that paediatric massive transfusion be defined as transfusion of more than 50% total blood volume (TBV) in 3 hours, transfusion of more than 100% TBV in 24 hours or transfusion support to replace ongoing blood loss of more than 10% TBV per minute.[380](#_ENREF_380) Given the age and weight-related variations in body mass and blood volume, transfusion volumes and the content of critical bleeding protocol packs should be adjusted for age or weight (or both).

Treating clinicians should be mindful that anticoagulant-preservative solutions affect acid–base status and can cause hypocalcaemia, and that hypothermia impairs global coagulation (including platelet function).

Institutions should develop a critical bleeding protocol specific for neonatal and paediatric patients that takes into account the following issues:

guidance on when to activate

who to contact and how to contact them (relevant phone numbers)

roles and responsibilities

prompts for safety measures, such as using large-bore cannulas where possible

age or weight-adjusted:

content of the critical bleeding protocol packs

volumes or doses of blood products used

definition of the products to be included in initial, second and subsequent packs (e.g. red cell concentrate, FFP, platelets and cryoprecipitate)

indications for or timing of cryoprecipitate use

when POC testing (TEG/ROTEM) is used, a definition of its role

definition of responsibilities for deactivation of critical bleeding protocol, with relevant contact information.

It may be useful to develop parallel protocols for laboratory and clinical management. The latter should include product dosing and administration at the bedside. The clinical pathway should include guidance on when to undertake laboratory testing, which tests to request, interpretation of results, and effect on product selection and dose.

|  |  |
| --- | --- |
| Expert opinion points – critical bleeding protocol | |
| EOP33 | Institutions that provide care for neonates and paediatric patients should have a critical bleeding protocol specific to such patients. |
| EOP34 | The critical bleeding protocol should outline the essential steps (including coordination and communication) to rapidly and effectively manage a patient who is at risk of or undergoing critical bleeding. |
| EOP35 | The critical bleeding protocol should include weight adjustments to guide blood product supply and administration. The clinician, in consultation with the haematologist or transfusion specialist, should tailor the type, volume and order of products given to the clinical circumstances. |
| EOP, expert opinion point | |

# 5 Future directions

The systematic review for this module found sufficient evidence to make recommendations for or against the use of a number of interventions in neonatal or paediatric patients or both. These included RBC transfusion, ESAs, hydroxyurea, FFP in cardiac patients, IVIg, prevention of hypothermia and antifibrinolytics. However, some of these recommendations were drawn from the evidence in adult populations. In others, although evidence from neonatal or paediatric populations supported a recommendation, further research is needed to strengthen that evidence or to improve guidance about its application. Furthermore, despite the potential for long-term consequences of neonatal and paediatric interventions, most studies addressed only short-term outcomes, which were often insufficient to determine the overall balance of risks and benefits.

The review has highlighted that there is insufficient high-quality evidence for when to use RBC transfusions in neonatal and paediatric populations, particularly among general medical and critically ill patients. It found insufficient evidence to make recommendations for clinical practice in several key areas, including:

the use of ESAs in children (other than preterm neonates)

the use of parenteral iron, FFP, fibrinogen concentrate and cryoprecipitate in children

thresholds for platelet transfusion and dose of platelets to administer in thrombocytopaenic patients.

In some research areas, gaps identified in this review are the subject of current research; for example:

the TOP trial[381](#_ENREF_381) and ETTNO trial[382](#_ENREF_382) will address the effect of transfusion thresholds in preterm and low birth weight infants

the TWiTCH trial[60](#_ENREF_60) will address questions relating to the use of hydroxyurea in SCD[[19]](#footnote-19)

the Planet 2 trial[143](#_ENREF_143) will address thresholds for platelet transfusion in preterm neonates.

There were numerous evidence statements where the evidence is uncertain or unknown. These areas, which are outlined below, may present avenues for further research.

## 5.1 Evidence gaps and areas for future research

There is a need for further research in the following areas:

in the neonatal and paediatric population in general:

the relative roles of cryoprecipitate, FFP and fibrinogen concentrate in the management of coagulopathy with or without bleeding

the appropriate dose of cryoprecipitate, FFP and fibrinogen concentrate in the management of coagulopathy with or without bleeding

the appropriate transfusion thresholds for platelet transfusion in the management of thrombocytopaenic patients with or without bleeding

the appropriate dose of platelets in the management of thrombocytopaenic patients with or without bleeding

the appropriate roles of factor concentrates in reducing RBC transfusion in the management of coagulopathy with or without bleeding

in preterm infants:

use of ESAs, using contemporary transfusion thresholds and addressing potential adverse effects and long-term outcomes

optimal dosing and timing of starting iron supplementation

the effect of RBC transfusion on the outcomes of BPD and NEC

the effect of ESA therapy on ROP, and on long-term outcomes and adverse events

the role of the *routine* use of deferred cord clamping

in neonates:

the use of deferred cord clamping where there is limited access to safe blood for transfusion or phototherapy for jaundice (this is particularly relevant to the Indigenous community because of the high level of IDA)

alternatives to deferred cord clamping (e.g. cord stripping or milking)

in infants with delayed onset of enteral feeding, the role of parenteral iron in terms of whether early intervention might prevent the need for later iron supplementation or reduce the incidence of transfusion, and what the long-term outcomes might be

in infants and children at risk for anaemia, the dose, duration, mode of administration, and long-term effects of iron supplementation

in paediatric patients with cancer, in the palliative care setting, the effects of ESAs on quality of life

in children with CKD, the long-term safety of ESAs

in paediatric patients with SCD:

the effect of hydroxyurea on stroke prevention (clinical and subclinical)

optimal strategies for identifying patients at high risk of silent and asymptomatic stroke

in paediatric patients who are chronically transfused (e.g. those with acquired or inherited bone marrow failure or anaemia syndromes), evidence to guide particular Hb thresholds

the effects of restrictive transfusions strategies in:

critically ill neonates

surgical patients

cardiac surgical patients

oncology patients

alloimmunisation in regularly transfused patients

in maternity patients, the use of IVIg to prevent HDFN

in neonates and infants undergoing surgery, the role of viscoelastometric POC testing

in paediatric patients undergoing spinal surgery, the role of reduced hypotension

in paediatric patients undergoing surgery in which substantial blood loss is anticipated, the role of:

ANH

intraoperative cell salvage

viscoelastometric POC testing

in patients with congenital or acquired bleeding disorders undergoing surgery, the use of antifibrinolytics

in paediatric patients of different age groups and in different surgical settings, the pharmacokinetics and dosing of antifibrinolytics

in paediatric patients, the use of miniaturised CPB systems compared to standard-sized systems.

# 6 Implementing, evaluating and maintaining the guidelines

## 6.1 Implementation strategies

The 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 messages.

Economic issues were considered when formulating the evidence-based recommendations within each module, and these recommendations will have cost implications. The NBA, together with the Jurisdictional Blood Committee (JBC) and key stakeholders, developed the *National Patient Blood Management Guidelines Implementation Strategy 2013–17*[383](#_ENREF_383) to facilitate uptake of the guidelines.

The implementation strategy includes the development of tools to support the introduction of 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 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*.[384](#_ENREF_384) 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*[385](#_ENREF_385) 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*.[386](#_ENREF_386) The National Education and Training (NEAT) Committee has been established to support the implementation of the strategy.[385](#_ENREF_385) 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.[387](#_ENREF_387) 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 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*[1](#_ENREF_1)in 2015–16.

## 6.2 Endorsement

A list of colleges and societies that have endorsed this module of the guidelines will be available on the NBA website.[[20]](#footnote-20)

## 6.3 Scheduled review and update

This module will be reviewed and amended in 2021 unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need for an earlier review. The outcomes of the pilot to update *Module 1 – Critical Bleeding/Massive Transfusion* in 2015–16 may mean that new methods and processes are available to update the PBM guidelines earlier than the scheduled 5-year review period.

The PBM Guidelines Project Manager at the NBA will convene the group of experts to undertake the review, and is the person to contact about major issues, events or practice changes.

To provide feedback and inform future reviews of this module, please send any comments on its content or implementation, or on the accompanying materials, to:

|  |  |
| --- | --- |
| Email: | guidelines@blood.gov.au |
| Mail: | Patient Blood Management Guidelines National Blood Authority Locked Bag 8430 Canberra ACT 2601 |
| Fax: | +61 2 6151 5300 |

Any correspondence will be forwarded to the project manager for consideration in the next scheduled review.

# Appendix A Governance

A1 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
* Clinical/Consumer Reference Groups (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 National Health and Medical Research Council (NHMRC) requirements.

The NBA provided the secretariat, project funding and projectmanagement. Section A3 of this appendix lists the membership of the bodies involved in governance of theguidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 6.

A1.1 Management framework for guideline development

Figure A1 illustrates the management framework used to manage the development of the six modules of the guidelines, described in Chapter 1.

Figure A1 Management framework for development of the guidelines

**Systematic reviewers and  
technical writer**

Contracted to NBA

Clinical direction from EWG and CRG

**Jurisdictional Blood**

**Committee**

**Clinical/Consumer**

**Reference Groups**

**Independent systematic review expert**

Contracted to NBA

Advice provided to

EWG and CRG

**National Blood Authority**

**PBM Steering Committee**

**Expert**

**Working Group**

CRG, Clinical/Consumer Reference Group; EWG, Expert Working Group; NBA, National Blood Authority; PBM, Patient Blood Management

A2 Terms of reference

Steering Committee

The overarching Steering Committee was originally established in 2009 to provide coordination and direction for development of the guidelines. In 2012–13, its role and membership was reviewed and a PBM Steering Committee was established to:

* provide information through the NBA to the Jurisdictional Blood Committee (JBC)

review resources that are developed as part of the PBM guidelines implementation strategy

provide expert advice on:

the design and delivery of PBM activities

PBM implementation and evaluation initiatives

System-based approaches to sustain PBM practices

the management, administration and use of fresh and other blood products excluding normal polyvalent immunoglobulin and clotting factors

education and training priorities

practice performance improvement

data and system requirements

influence the uptake of PBM practice

improve intergovernmental coordination and cooperation on PBM implementation activities

monitor guideline development projects to ensure they meet their objectives

link the PBM program activities to deliver the priorities for the *National Safety and Quality Health Service (NSQHS) Standards*[384](#_ENREF_384)

integrate the PBM program with the Australian Commission on Safety and Quality in Health Care (ACSQHC) initiatives for delivery to health providers and their safety and quality framework

network with other NBA committees to share information.

Expert Working Group

The EWG was established in 2008 to advise the original Steering Committee about the scope and structure of the guidelines, and determine the focus the systematic review of the literature. In 2012–13, its role and membership was reviewed and the new terms of reference were to provide advice to the NBA on the scope of the modules, and approve the focus of the systematic review questions and literature search strategies. Each member of the EWG is responsible for overseeing the conduct of the systematic review in relation to their area of practice as either a member or Chair of the relevant CRG. Each EWG member is responsible for ensuring that the scope of the modules is appropriate, and that they address areas of clinical need.

The role of the EWG is to:

* formulate the generic clinical questions to be answered in all modules by the literature review (under the guidance of the systematic reviewers)
* identify the need for CRGs, participating in or chairing these groups as required, and identifying and nominating additional CRG members as required
* consider the specific clinical questions and systematic review specifications developed by the CRGs and, if necessary, make recommendations to the NBA on revisions
* consider the scope of the project as referred by the CRGs and, if necessary, make recommendations to the NBA on revisions
* consider and provide advice to the NBA as to whether interests declared by Chairs of the CRGs present a conflict and suggest strategies to manage these declarations

consider and provide advice, as requested by CRG Chairs, about interests declared by members of the CRG, to assist the Chair to manage declared interests to minimise potential bias in clinical practice guidance.

Clinical/Consumer Reference Groups

The CRGs provide clinical and consumer input to the systematic review, draft the module and provide guidance on relevant additional clinician and consumer information. The role of each CRG is to:

under the guidance of the systematic reviewers, formulate the specific clinical question for their module

under the guidance of the systematic reviewers, define the literature search strategies for all the clinical questions

review the medical literature

provide advice on current practice in their area of expertise

under the guidance of the systematic reviewers and medical writer, formulate evidence-based recommendations based on the results of the review

under the guidance of the systematic reviewers and medical writer, formulate practice points based on expert consensus opinion

under the guidance of the systematic reviewers, ensure their analysis and grading of the literature and recommendations follows NHMRC procedures and meets the 2011 standards

define the structure of the module

take responsibility for drafting content of the module in their area of expertise (as assigned by the Chair and agreed by all members)

under the guidance of the systematic reviewers and medical writer, draft the content of the module

review public consultation feedback and make changes as required

propose relevant additional clinician and consumer materials

propose tools and strategies to support implementation.

Consumer selection process

An open recruitment process was used to seek interested consumers to participate on the CRG. The consumer representative and Indigenous representative positions were advertised on the NBA website, and forwarded to the Consumer Health Forum and major consumer organisations in each state and territory in Australia. Applications were reviewed by the NBA Executive Director – Fresh, Data and Clinical Development, Director – Blood Sector Clinical Development, PBM Guidelines Project Manager, and the Chair of the CRG. Upon notification and acceptance of their selection on the group, the representatives were provided with an orientation pack, and a face-to-face meeting was held (where possible) before the first meeting. The following documentation was provided:

an abbreviations and definitions list (including NHMRC and systematic review terminology)

a summary of the blood sector governance structure and major stakeholders

an overview of the Australian health-care system

frequently asked questions (FAQ): ‘What are the PBM guidelines?’

an overview of the NBA

a background on the PBM guidelines

NHMRC tables:

levels of evidence hierarchy

ratings for the body of evidence

grades for recommendations

hard copies of each previous module

links to relevant pages and documents about PBM on the NBA website.

Systematic reviewers and technical writers

The NBA contracted systematic reviewers and technical writers to conduct systematic reviews of the scientific literature, and provide technical writing services to produce each module and associated deliverables, including technical reports.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

|  |  |
| --- | --- |
| Dr 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 |
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| Ms Lauren Porter | Consumer representative | Not applicable |
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|  |  |
| --- | --- |
| Transfusion Practice and Education team at the Blood Service | For the adaptation of the adult iron calculation tool (included in the background research) |
| Dr David Sutton | IV iron protocol templates courtesy of the Royal Children’s Hospital, Melbourne |

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| Dr Hilary Cadman | Cadman Editing Services (independent contractor to Optum) |

# Appendix B Process report

B1 Development process and methodology

Further information on the development process and methods is included in Chapters 1 and 2, and Appendix A.

B2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EWG and the CRG for this guideline, and further refined through consultation among the systematic reviewer, CRG, NBA and independent systematic review expert. These processes are outlined in further detail in Chapter 1 and Appendix A.

B3 Methodology

Methods are outlined in Chapter 2, with greater detail given in the technical reports.[388-389](#_ENREF_388)

B4 Consensus process

Consensus process for developing practice points and expert opinion

In circumstances where no evidence was identified, practice points were developed by the CRG through a consensus-based process. Where relevant guidance that was outside of the scope of the systematic review was required, consensus-based ‘expert opinion’ was included (e.g. background research in Chapter 4).

Guiding principles and values, and ‘ground rules’ were established, and the following process was used to develop practice points and expert opinion through consensus.

**Stage 1 – Introduction.** The Chair described the consensus process, participants’ roles and responsibilities, ground rules and the guiding principles.

**Stage 2 – Open discussion.** The Chair opened the floor to a general discussion and suggestions for practice point/expert opinion wording. The Chair provided an opportunity for concerns or issues to be raised.

**Stage 3 – Resolve concerns.** The Chair had the first option to resolve the listed concerns by clarifying or changing the wording, or seeing whether those with concerns will stand aside (i.e. ‘had concerns, but could live with them’). Where concerns were not resolved and the time was short, the discussion was carried over to a later meeting.

**Stage 4 – First call for consensus.** The Chair called for consensus.

**Stage 5 – Second call for consensus.** If consensus was not reached, the CRG considered the consensus process guiding principles and values, and:

the member withdrew the concern and consensus was reached

the member stood aside and the differing schools of thought were documented

the member was not willing to withdraw the concern or stand aside, and the CRG declared itself blocked – the practice point or expert opinion was not accepted.

B5 Conflict of interest

All members of the PBM Steering Committee, CRG, 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 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:

1. is an actual or perceived conflict of interest
2. requires disclosure to the other members
3. can be managed without jeopardising the rigorous methodology process and accurate reporting of the evidence in the guidelines
4. requires the member to be excluded from certain or all discussions, or
5. 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.

The declarations listed below were made during the guideline development process.

|  |  |
| --- | --- |
| A/Prof Donald Bowden | A/Prof Bowden received research support and partial sponsorship to the American Society of Haematology Annual Scientific Meeting from Novartis Pharmaceuticals. |
| Dr Gemma Crighton | Nil. |
| Mr Shannon Farmer | Mr Farmer is a consultant in PBM and from 2006–2013 was a contracted consultant to the Western Australia Department of Health Patient Blood Management Program. He has received lecturing/consulting honoraria or travel support from:  • AdvancMed (USA)  • Australian JBC  • Australian NBA  • Australia Pacific Health Group  • Australian Red Cross Blood Service  • Beijing Municipal Health Bureau (China)  • Department of Health New South Wales  • Department of Health Queensland  • Department of Health South Australia  • Department of Health Western Australia  • Janssen-Cilag (Australia)  • Haematology Society of Australia and New Zealand/Australia  • Johnson & Johnson, ETHICON Biosurgery (Australia, Europe, Asia Pacific & USA)  • Medical Society for Blood Management (Europe)  • Medtel Pty Ltd (Australia)  • National Blood Authority (Australia)  • Australian & New Zealand Society of Blood Transfusion (Australia)  • Novo Nordisk (Australia)  • Society for the Advancement of Blood Management (USA)  • Vifor Pharma (Europe).  In 2008 he served on J&J ETHICON Biosurgery International Ad Board for PBM. He is a chief investigator and a principal investigator for two State Health Research Advisory Council (SHRAC) research grants:  • Primary care and tertiary care clinicians working with patients to ensure they are “Fit for Surgery”  • **I**ntravenous i**R**on or placeb**O** for a**N**ae**M**i**A** in i**N**tensive care: a randomised controlled study: The IRONMAN Study.  He is also an associate investigator for one NHMRC research grant:  • Patient Blood Management in Critical Illness and Trauma.  He is a Board Member and General Secretary for the Medical Society for Blood Management and a member of two international professional societies: Society for the Advancement of Blood Management (SABM) and Network for the Advancement of Transfusion Alternatives (NATA). He is also a Board Member for the Australasian Association for Blood Conservation.  He has received lecture honorarium. Fremantle General Practice Network, Western Australia. Honorarium for Book Chapter, Thieme, Stuttgart, Germany. Honorarium for Book Chapter, Elsevier Science, USA.  Mr Farmer was also on an Expert Panel, European Commission, European Guide on “Good Practices in the Field of Blood” and “European Union Guide for Member States on Good Practices for Patient Blood Management (EU-PBM).” Consumers, Health and Food Executive Agency (CHAFEA) of the European Commission. |
| Dr Chris Fraser | Nil. |
| A/Prof Craig French | A/Prof French received research funding from Wyeth between 2004 and 2008 provided to Western Health while he was an employee. He was a chief investigator on the TRANSFUSE and Erythropoietin in Traumatic Brain Injury studies, both of which received project grant funding from the NHMRC. He has also received research grants from the NHMRC, Health Research Council of New Zealand (HRCNZ), Eli Lilly and Bayer. He was appointed to the Australian Red Cross Blood Service Advisory Board in 2011 and as a Blood Service Fellow in 2012. |
| Dr Glenn Gardiner | Dr Gardiner has received travel grants from GE, Philips and STOR2 all related to obstetric imaging and fetal therapy.  Dr Gardiner also has shares in CSL. |
| Dr Susan Hale | Nil. |
| A/Prof Helen Liley | A/Prof Liley received travel, accommodation and registration from the NBA and the Australian Government Department of Health, for the Western Australian Patient Blood Management Conference in Perth in 2014, to present a talk: ‘What about the Children – is there a place for PBM in their care?’  A/Prof Liley is the Mater Mothers’ Hospital site principal investigator on the NHMRC-funded randomised controlled trial Australian Placental Transfusion Study (APTS), which is examining timing of cord clamping in very low birth weight infants. |
| Prof Rhonda Marriott | Prof Marriott is the Aboriginal and Torres Strait Islander representative chief investigator on a NHMRC-funded project that will also investigate anaemia in Aboriginal children titled “Improving primary care for Aboriginal mothers and babies in the Kimberley region of Western Australia: a population and region based cluster randomised trial driven by local health service providers.” |
| Ms Lauren Porter | Nil. |
| Dr Sylvio Provenzano | Dr Provenzano was involved in a project studying potential benefit of cell salvage in patients under 6kgs. No financial or technical support from any company. |
| Prof Linda Shields | Nil. |
| Dr Michael Stark | Nil. |
| Dr Christian Stocker | Nil. |
| Dr Amanda Thomson | Dr Thomson is an employee of the Australian Red Cross Blood Service and BloodSafe eLearning Australia. |
| Dr Bronwyn Williams | Nil. |

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.

B6 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 NBA website.[[21]](#footnote-21) 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 CRG. An email was sent to the following:

members of each of the previous and current EWG, CRGs, independent systematic reviewer, Haemovigilance Advisory Committee, National Education and Training Committee and 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.

XX 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.

B7 Finalising the guidelines

AGREE II assessment

The *Appraisal of Guidelines for REsearch & Evaluation* (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.[390](#_ENREF_390) 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 would recommend *[recommendation will be inserted following public consultation]*.

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 NHMRC requirements for externally developed guidelines. The module and accompanying documents were then sent to the NHMRC for methodological and independent peer review on DATE.

NHMRC approval

Approval from the NHMRC was received on [DATE].

# Appendix C Transfusion risks in the context of patient blood management

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 non-viral 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, thrombocytopaenia 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.

Table C.1 summarises transfusion risks, and Table C.2 presents the Calman Chart, which may be useful to clinicians for explaining risks to patients.[391](#_ENREF_391)

Table C.1 Transfusion risks

|  |  |  |
| --- | --- | --- |
| Transfusion risk | Estimated ratea  (highest to lowest risk) | Calman ratingb |
| Transfusion-associated circulatory overload (iatrogenic) | Up to 1 in 100 transfusions | High |
| Transfusion-related acute lung injury | 1 in 1200–190,000 | Low to minimal |
| Haemolytic reactions | Delayed: 1 in 2500–11,000  Acute: 1 in 76,000  Fatal: Less than 1 in 1.8 million | Low to very low  Very low  Negligible |
| Anaphylactoid reactions or anaphylaxis  (usually due to IgA deficiency) | 1 in 20,000–50,000 | Very low |
| Bacterial sepsis: platelets | At least 1 in 75,000 | Very low |
| Bacterial sepsis: red blood cells | At least 1 in 500,000 | Minimal |
| Hepatitis B virus | Approximately 1 in 468,000 | Minimal |
| Hepatitis C virus | Less than 1 in 1 million | Negligible |
| Human immunodeficiency virus | Less than 1 in 1 million | Negligible |
| Human T-lymphotropic virus (types 1 and 2) | Less than 1 in 1 million | Negligible |
| Malaria | Less than 1 in 1 million | Negligible |
| Variant Creutzfeldt-Jakob disease (not tested) | Possible, not yet reported in Australia | Negligible |
| Transfusion-associated graft-versus-host disease | Rare | Negligible |
| Transfusion-related immune modulation | Not quantified | Unknown |

IgA, immunoglobulin A  
**a** Risk per unit transfused unless otherwise specified  
**b** See Calman 1996[391](#_ENREF_391)   
Source: Australian Red Cross Blood Service website (www.transfusion.com.au, accessed 28 July 2014)   
Note: The above estimates may change over time. See the Australian Red Cross Blood Service website ([www.transfusion.com.au](http://www.transfusion.com.au)) for the most recent risk estimates.

Table C.2 Calman Charta (United Kingdom risk per 1 year)

|  |  |  |
| --- | --- | --- |
| Rating | Rate | Example |
| Negligible | ≤1 in 1,000,000 | Death from lightning strike |
| Minimal | 1 in 100,000–1,000,000 | Death from train accident |
| Very low | 1 in 10,000–100,000 | Death from an accident at work |
| Low | 1 in 1,000–10,000 | Death from a road accident |
| Moderate | 1 in 100–1,000 | Death from smoking 10 cigarettes per day |
| High | ≥1 in 100 | Transmission of chicken pox to susceptible household contacts |

**a**See Calman 1996[391](#_ENREF_391)

# Appendix D Blood sectors

D1 Australian blood sector

Council of Australian Governments Health Council

The Council of Australian Governments (COAG) promotes policy reforms that are of national significance, or that need coordinated action by all Australian governments. The COAG Health Council (CHC) comprises health ministers from all jurisdictions, and is one of eight COAG Councils. The Commonwealth and state and territory health ministers on the CHC work in partnership to improve health outcomes for all Australians, and ensure the sustainability of the Australian health system.

The CHC’s responsibilities include the oversight and management of the Australian blood sector, including national policy and financial decisions in relation to the supply of blood and blood products, and the determination of which products and services can be bought with public funds. The CHC oversees the implementation of the National Blood Agreement (described below), and is supported in its roles by the Australian Health Ministers’ Advisory Council (AHMAC).

**Australian Health Ministers’ Advisory Council**

AHMAC provides support to the CHC. It advises the health ministers on strategic matters relating to the coordination of health services across the nation and, as necessary, with New Zealand. The AHMAC considers blood sector matters referred to it by the Jurisdictional Blood Committee (JBC) through the Hospitals Principal Committee, and reports as necessary to the CHC. The AHMAC has no statutory power, and decisions are reached by consensus.

Hospitals Principal Committee

The Hospitals Principal Committee considers and provides advice to the AHMAC on a range of issues. Areas covered include:

all activities that largely relate to hospital care including emergency departments, outpatient care, inpatient care and alternatives to hospital care

implementation of the health reform agenda as it applies to hospital care

clinical, technical and medicoethical developments

the appropriateness, likely impact, policy implications, effectiveness and safety of clinical and technical developments.

Jurisdictional Blood Committee

All Australian governments are represented on the JBC, which was established by the National Blood Agreement in 2003.[392](#_ENREF_392) The committee:

is the conduit between governments and the NBA

represents the Australian state and territory governments’ positions on:

blood policy, demand, supply planning and product distribution

funding

evidence-based approaches to emerging products, services and technologies

oversees the NBA’s role in blood supply contracting.

The committee is the primary body responsible for providing advice and support on these matters to the CHC through the AHMAC.

National Blood Authority

The NBA was established in 2003 as an Australian Government agency within the health and ageing portfolio. It is responsible for ensuring the adequate, safe, secure and affordable supply of blood and blood products. The role of the NBA is outlined in the *National Blood Authority Act 2003* and the National Blood Agreement.

Part 5 of the National Blood Agreement requires the development and implementation of specific safety and quality strategies, including development, implementation and review of evidence-based national clinical practice guidelines for blood, blood products and blood-related services. The aim is to encourage best practice in the management and use of such products and services.

Therapeutic Goods Administration

The Therapeutic Goods Administration is the regulator for blood and blood products in Australia, and is responsible for:

regulating the sector in terms of the safety and quality of blood and blood products under the *Therapeutic Goods Act 1989*

auditing good manufacturing practice

issuing product recalls

modifying safety standards

issuing directives such as donor deferral.

Australian Red Cross Blood Service

The Australian Red Cross Blood Service was established as a national organisation in 1996. It is responsible for collecting, processing and distributing blood and blood components sourced from voluntary donors in Australia. The Australian Red Cross Blood Service works alongside Australian regulators, government departments, and commercial and professional organisations, and with international bodies, to constantly review and improve the safety and provision of blood and blood components in Australia. The Australian Red Cross Blood Service also has significant transfusion medicine expertise and clinical involvement.

D2 New Zealand blood sector

Ministry of Health

The New Zealand Minister of Health is the government owner of the New Zealand Blood Service (NZBS). The Minister appoints the NZBS Board and approves the Statement of Intent and Output Agreement.

The Ministry of Health monitors the performance of the NZBS, and works closely with the organisation in setting the overall strategic direction for the provision of blood and blood products in New Zealand.

Medsafe

Medsafe is the regulator for blood and blood products in New Zealand. Medsafe is responsible for:

* regulating the sector in terms of the safety and quality of blood and blood products under the *Medicines Act 1981* and *Medicines Regulations 1984*
* auditing and licensing blood centres in accordance with good manufacturing practice
* issuing product recalls
* approving changes to the NZBS Collection and Manufacturing Standards.

New Zealand Blood Service

The NZBS is a Crown Entity established under the *New Zealand Public Health and Disability Act 2000*. Its legislated purpose and core activity is the safe, timely, high-quality and efficient provision of blood and blood products to clinicians for the people of New Zealand. It also provides related services, including matching of patients and donors before organ or tissue transplantation, and provision of tissue banking (skin, bone and stem cell services).

The NZBS Board is appointed by, and responsible to, the Minister of Health, and performs strategic and governance functions in accordance with the Act.

The NZBS works closely with regulators, the Ministry of Health and international agencies to monitor international developments in the field of transfusion medicine, to develop national policies and to implement them as appropriate in the New Zealand setting.

In addition to its role in collecting, processing and distribution of blood and blood products, the NZBS is actively involved in the provision of blood banking and clinical services within New Zealand’s major hospitals.

# Appendix E Product information

For information on blood products available in Australia, see the website of the Australian Red Cross Blood Service ([www.transfusion.com.au](http://www.transfusion.com.au)).

For information on blood products available in New Zealand, see the website of the New Zealand Blood Service ([www.nzblood.co.nz](http://www.nzblood.co.nz/)).

# Appendix F RBC transfusions in preterm infants

This appendix provides clinical guidance from the Clinical/Consumer Reference Group (CRG) on haemoglobin (Hb) thresholds for transfusion of preterm infants.

In the absence of clear evidence from high-quality trials, there is wide variation in such thresholds in international practice, as demonstrated by a recent survey of 1018 neonatologists in 22 countries.[393](#_ENREF_393) For infants of extremely low birth weight or <28 week gestation, most neonatologists favoured Hb thresholds for transfusion of 95–120 g/L for infants not receiving mechanical ventilation, then decreasing thresholds over subsequent weeks. They favoured higher thresholds for infants receiving increased respiratory support in the form of supplemental oxygen.

New information is expected from large randomised controlled trials that are currently underway. Meanwhile, the CRG suggests that the values given in Table F.1 represent a reasonable approach to transfusion thresholds for preterm infants.

Table F.1 Haemoglobin threshold for preterm infants

|  |  |  |
| --- | --- | --- |
| Postnatal week | Hb (g/L) | |
| No respiratory support | Respiratory support (e.g. supplemental oxygen, high-flow nasal cannula, CPAP, positive-pressure ventilation) |
| 1 | 100–120 | 110–130 |
| 2 | 85–110 | 100–125 |
| ≥3 | 70–100 | 85–110 |

CPAP, continuous positive airway pressure; Hb, haemoglobin

The threshold for transfusion within these ranges may be influenced by the presence of symptoms and other factors such as:

anticipated blood loss (e.g. haemolysis, phlebotomy or surgery)

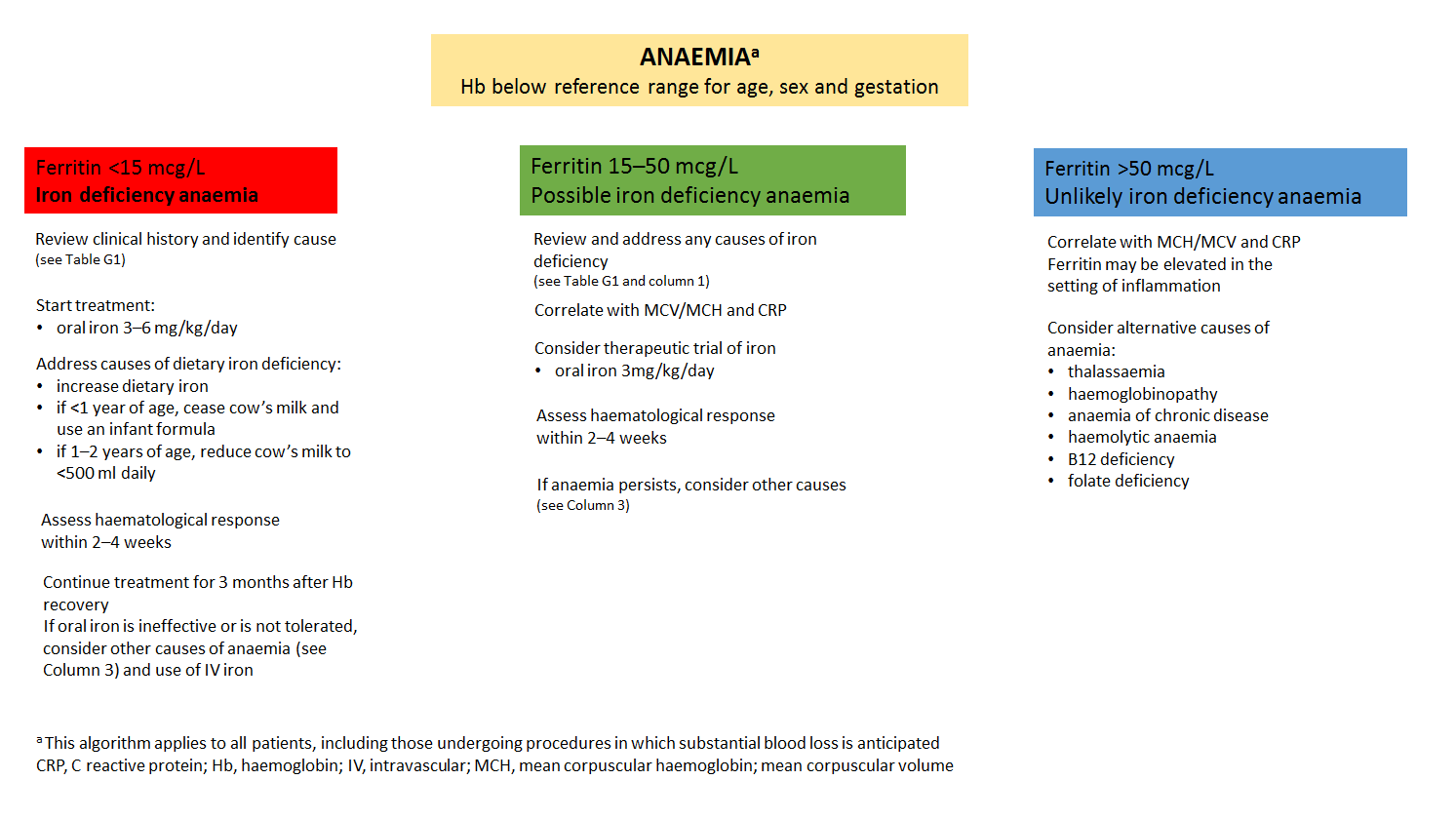
quality of nutrition

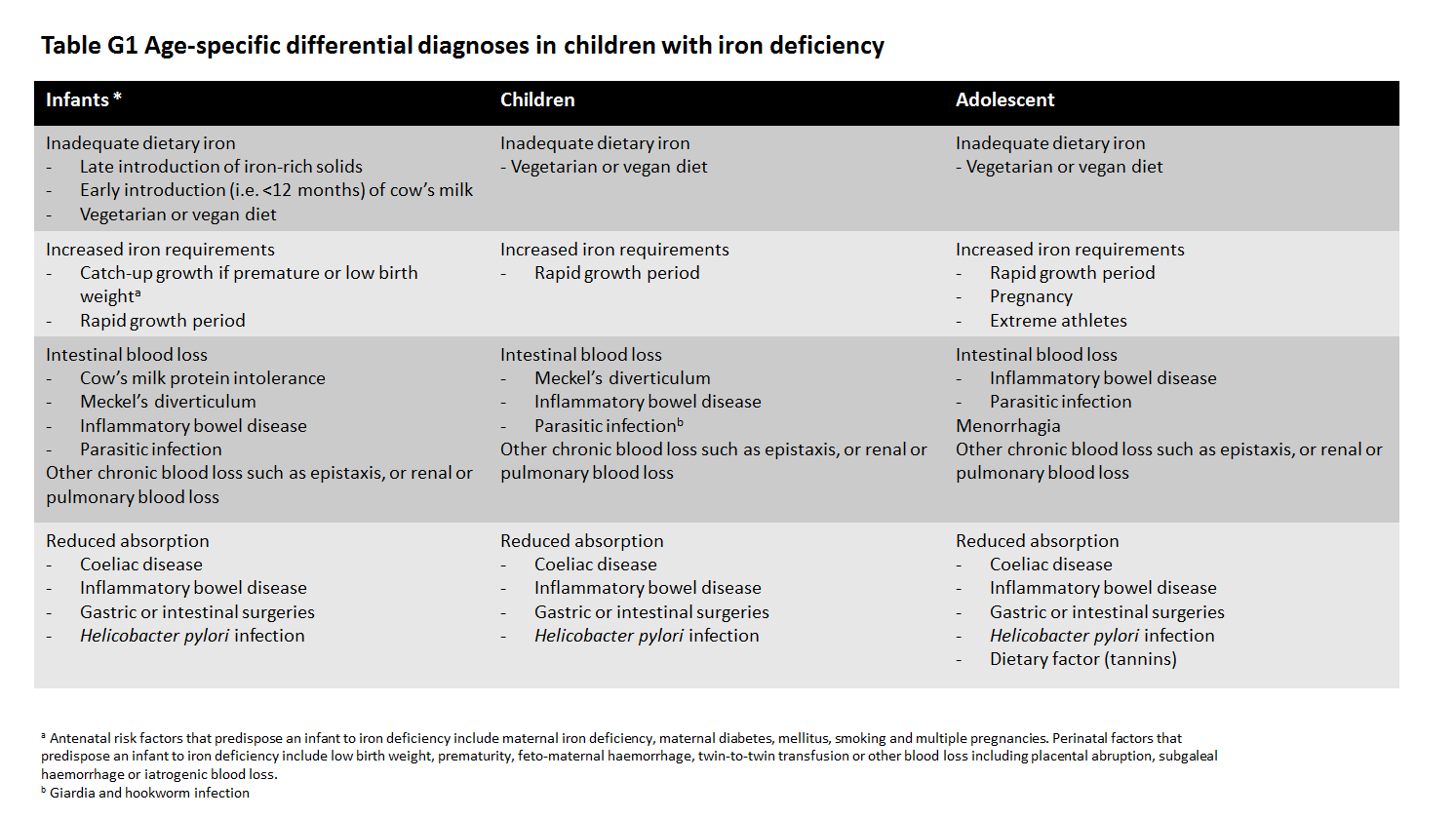
severity of illness

site of sampling – Hb measured on blood samples obtained from a large artery or from veins tends to be lower than that from free-flowing capillary samples.[394](#_ENREF_394)

In general, the decision to transfuse should be based on laboratory measurement of Hb rather than on estimates obtained from blood gas analysers, except in cases of clinical urgency. For guidance in calculating volume to transfuse, see Appendix J.

# Appendix G Paediatric haemoglobin assessment and optimisation template





# Appendix H Tranexamic acid dosing guidance

This appendix provides guidance from the Clinical/Consumer Reference Group (CRG) on tranexamic acid (TXA) dosing in various paediatric patient groups. Evidence for appropriate paediatric dosing is available for craniofacial surgery,[203](#_ENREF_203) and pragmatic dosing regimes are suggested for trauma[395](#_ENREF_395) and scoliosis surgery,[183](#_ENREF_183) but not for cardiac surgery, as explained below.

H1 Surgery other than cardiac

Table H1 Guidance on tranexamic dosing in surgical paediatric patients other than cardiac

|  |  |  |
| --- | --- | --- |
| Patient group | Loading dose (mg/kg over 10 minutes, up to a maximum of 1 g) | Infusion (mg/kg/hour) |
| Traumaa | 15 | 2 |
| Craniofacial surgery | 10 | 5 |
| Scoliosis surgery | 10 | 5 |

a Commencing within 3 hours of trauma and continuing for at least 8 hours or until bleeding stops

H2 Cardiac surgery

There is a lack of evidence for appropriate target plasma concentrations for TXA in paediatric cardiac surgery; hence, no specific guidance on dosing can be given for this patient group. However, a safe and effective dose regimen is likely to need to take into account factors such as age, weight, pump prime volume and use of ultrafiltration. A loading dose followed by a continuous infusion is more likely than intermittent boluses to produce stable plasma concentrations.[212](#_ENREF_212)

# Appendix I Intravenous Iron

I1 Introduction

I1.1 Purpose

To ensure safe and appropriate administration of intravenous (IV) iron polymaltose, iron sucrose and iron carboxymaltose.

I1.2 Procedure

Check for previous adverse reactions to IV iron before commencing infusion.

Ensure that child and parent understand procedure:

obtain verbal consent to procedure

ensure that child and parent are aware of possible adverse reactions.

Ensure that medication and treatment orders are correctly written up by the medical officer.

Ensure that oxygen and resuscitation equipment are in working order.

Ensure that there is an order for PRN adrenaline 0.01 mg/kg intramuscular (IM) 1:1000 in the event of anaphylaxis.

Establish patient IV access and ensure that the IV is working well.

Take blood specimens as requested.

Commence infusion and observations as per protocol.

Monitor for any local or systemic adverse reactions.

If there are signs of an adverse reaction or anaphylaxis, cease the infusion immediately.

Contact the treating medical officer or call the medical emergency team (MET).

Treat symptomatically, and administer oxygen, IV fluids and adrenaline as required.

I1.3 Precautions

Ensure that all staff are familiar with MET criteria and can recognise when to initiate an MET call.

Do not administer iron infusions out of hours unless they are urgently required and staffing levels are appropriate.

Place the patient in a clinical area where the patient can be closely monitored throughout the duration of the infusion.

Ensure that patients undergoing iron infusions are not on oral iron therapy, and that they do not recommence oral iron therapy until 1 week after the last dose of parenteral therapy.

For iron sucrose and iron polymaltose:

consider premedications:

* + - ceterizine (0.125 mg/kg oral; maximum 10 mg)
    - hydrocortisone (2–4 mg/kg IV; maximum 100 mg)

be aware that concomitant therapy with an angiotensin-converting enzyme (ACE) inhibitor may increase the incidence of adverse effects.

I1.4 Contraindications

Previous allergic reactions to iron therapy.

Severe liver dysfunction.

Iron overload.

II1.5 Observations

Baseline weight.

Baseline temperature, respiratory rate, pulse and blood pressure.

Direct observation for the first 15 minutes.

For the remainder of the infusion, observe:

blood pressure every 15 minutes

heart rate for 60 minutes then hourly.

Monitor for signs of anaphylaxis, headache, nausea, hypotension, joint and muscle pain or signs of extravasation.

I1.6 Discharge

Ensure patient meets discharge criteria.

ALERT

* Check prescription and vials carefully as there are many different forms of IV iron preparations.
* Iron formulations have different iron concentrations, maximum doses, dilutions and rates of administration and are not interchangeable with regard to dose, dilution and rates of administration.

I2 Iron carboxymaltose (Ferinject) dose[396](#_ENREF_396)

Total or cumulative dose – may need to be administered over several doses at weekly intervals.

Maximum dose – 20 mg/kg/week (to a maximum of 1000 mg).

Two ampule sizes:

100 mg/2 mL

500 mg/10 mL.

Dilute using 0.9% sodium chloride:

maximum concentration 5 mg/mL

minimum concentration 2 mg/mL.

For children under 14 years of age, use a maximum dose of 20 mg/kg and round down to the nearest ampoule.

Administer over at least 15 minutes.

Table I-1 Total dose (mg of IV iron carboxymaltose) based on Hb concentration and body weight

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hb (g/L)a | Weight (kg) | | | | | | | | | | | |
| 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 |
| 60 | 1200 | 1300 | 1400 | 1500 | 1600 | 1700 | 1900 | 2100 | 2200 | 2300 | 2400 | 2500 |
| 75 | 1100 | 1200 | 1300 | 1400 | 1400 | 1500 | 1600 | 1800 | 1900 | 2000 | 2100 | 2200 |
| 90 | 1000 | 1000 | 1100 | 1200 | 1200 | 1300 | 1400 | 1600 | 1600 | 1700 | 1800 | 1800 |
| 105 | 800 | 900 | 900 | 1000 | 1000 | 1100 | 1200 | 1300 | 1400 | 1400 | 1500 | 1500 |

a Maximum dose per infusion is 20 mg/kg/week  
Source: Royal Children’s Hospital (2013)[396](#_ENREF_396)

I3 Iron sucrose (Venofer) dose[397](#_ENREF_397)

Dose (ml) of iron sucrose – 20 mg/mL.

Ampule of 5 mL is equivalent to 100 mg of iron.

Maximum dose – 100 mg not more than three times per week.

Dilute with 0.9% sodium chloride to a maximum concentration of 1 mg/mL.

Commence at 40 mL/hour for the first 50 mL.

Then increase by 20 mL/hour every 15 minutes, to a maximum of 100 mL/hour.

Table I-2 Dose (mL of IV iron sucrose) based on Hb concentration and body weight

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hb (g/L)a |  | Body weight (kg) | | | | | | | | | | | | | | | | | |
|  | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 |
| 60 | mL | **8** | **16** | **24** | **32** | **40** | **48** | **63** | **68** | **74** | **79** | **84** | **90** | **95** | **101** | **106** | **111** | **117** | **122** |
| 75 | mL | **7** | **14** | **21** | **28** | **35** | **42** | **57** | **61** | **66** | **70** | **75** | **79** | **84** | **88** | **93** | **97** | **102** | **106** |
| 90 | mL | **6** | **12** | **19** | **25** | **31** | **37** | **50** | **54** | **57** | **61** | **65** | **68** | **72** | **75** | **79** | **83** | **86** | **90** |
| 105 | mL | **5** | **11** | **16** | **21** | **26** | **32** | **44** | **47** | **49** | **52** | **55** | **57** | **60** | **63** | **66** | **68** | **71** | **74** |

a Maximum dose 100 mg not more than three times per week.  
Source: Royal Children’s Hospital (2012)[397](#_ENREF_397)

Use Hb closest to patient’s Hb.

Doses coloured blue may be diluted in 250 mL of 0.9% sodium chloride.

Doses coloured red may be diluted in 500 mL of 0.9% sodium chloride.

Doses coloured purple need dilution in 1000 mL of 0.9% sodium chloride.

I4 Iron polymaltose (Ferrosig) dose[398](#_ENREF_398)

Dose (mL) of iron polymaltose 50 mg/mL.

Ampule = 2 mL of iron polymaltose = 100 mg of iron.

Maximum dose 2500 mg/infusion.

Dilute with 0.9% sodium chloride to a maximum concentration of 5 mg/mL.

Standard infusion (500 mL 0.9% saline):

commence infusion at 40 mL/hour for 75 minutes (50ml)

then increase by 20 mL/hour 15 minutely to a maximum rate of 120 mL/hour.

For smaller patients or fluid restricted (250 mL 0.9% saline):

commence infuse at 20 mL/hour for 75 minutes (25 mL)

then grade up by 10 mL/hour to a maximum rate of 60 mL/hour.

Table I-3 Dose (mL of IV iron polymaltose) based on Hb concentration and body weight

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hb (g/L)a |  | Body weight (kg) | | | | | | | | | | | | | | | | | |
|  | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 |
| 60 | mL | **3** | **6** | **10** | **13** | **16** | **19** | **25** | **27** | **30** | **32** | **34** | **36** | **38** | **40** | **42** | **45** | **47** | **49** |
| 75 | mL | **3** | **6** | **9** | **11** | **14** | **17** | **23** | **24** | **26** | **28** | **30** | **32** | **33** | **35** | **37** | **39** | **41** | **43** |
| 90 | mL | **3** | **5** | **7** | **10** | **12** | **15** | **20** | **22** | **23** | **24** | **26** | **27** | **29** | **30** | **32** | **33** | **34** | **36** |
| 105 | mL | **2** | **4** | **6** | **8** | **11** | **13** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** |

a Maximum dose 2500 mg/infusion  
Source: Royal Children’s Hospital (2012)[398](#_ENREF_398)

Use Hb closest to patient’s Hb.

Doses coloured **blue** may be diluted in 250 mL of 0.9% sodium chloride.

Doses coloured **red** may be diluted in 500 mL of 0.9% sodium chloride.

Doses coloured **purple** need dilution in 1000 mL of 0.9% sodium chloride.

# Appendix J Transfusion volume calculation for neonates, infants and small children

In calculating transfusion volume for neonates, infants and small children:

the dose or transfusion volume of blood components for neonates, infants and children should be carefully calculated and prescribed in mL (not in ‘units’), with a specified transfusion rate

an administration rate of up to 6 mL/kg/hour (for a 20 mL/kg transfusion) or 5 mL/kg/hour (for a 15 mL/kg transfusion) will allow proper checking procedures and completion of the transfusion within the 4 hours that RBCs can be out of a blood refrigerator.

Transfusion volume can be calculated using the following formula:[399](#_ENREF_399)

Transfusion volume (mL) = patient’s weight x EBV × (desired Hb – patient’s Hb) / Hb of donor unit

where:

weight is in kg

the patient’s estimated blood volume (EBV) is in mL/kg – this decreases with age, from 100–120 mL/kg in extremely preterm infants, to 80–85 mL/kg in term infants and about 70 mL/kg in older infants and children

haematocrit (Hct) can be substituted for Hb in the formula, provided it is used throughout; Hb can be estimated from Hct using the formula Hb = Hct × 1000/3

Table J.1 Hct values

|  |  |
| --- | --- |
| Cell type | Hct ± SD [range] |
| Paediatric RBCs leucocyte depleted | 0.63 ± 0.03 [0.5–0.7] |
| RBCs leucocyte depleted | 0.59 ± 0.03 [0.5–0.7] |

Hct, haematocrit; RBC, red blood cell; SD, standard deviation  
Source: Australian Red Cross Blood Service data (1 July 2013 to 30 June 2014)[[22]](#footnote-22)

#### Neonates

In neonates typical transfusion dose is 10–20mL/kg (where the upper end of the range applies to severe anaemia, expected ongoing risk factors or concurrent bleeding)

Table J.2 Approximate Hb increments that can be expected for transfusion

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimated Hb (g/L) after transfusion | | |
| Current Hb (g/L) | Transfusion of  10 mL/kg | Transfusion of  15 mL/kg | Transfusion of  20 mL/kg |
| Very preterm infant with estimated blood volume 100 mL/kg | | | |
| 70 | 91 | 102 | 112 |
| 80 | 101 | 112 | 122 |
| 90 | 111 | 122 | 132 |
| Term infant with estimated blood volume 80 mL/kg | | | |
| 70 | 96 | 109 | 123 |
| 80 | 106 | 119 | 133 |
| 90 | 116 | 129 | 143 |

Hb, haemoglobin

#### Infants and children less than 20 kg

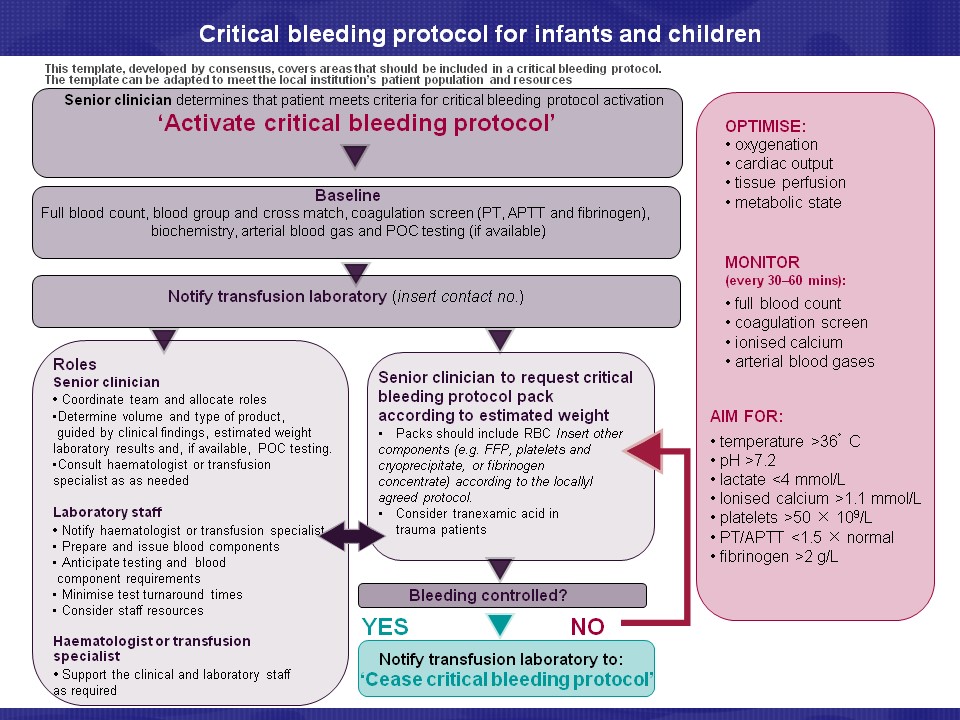
In infants and children less than 20 kg, blood volume and Hb of donor unit are usually estimated to be similar for all patients, rather than varying transfusion by transfusion. Therefore, the formula can be simplified to the following:

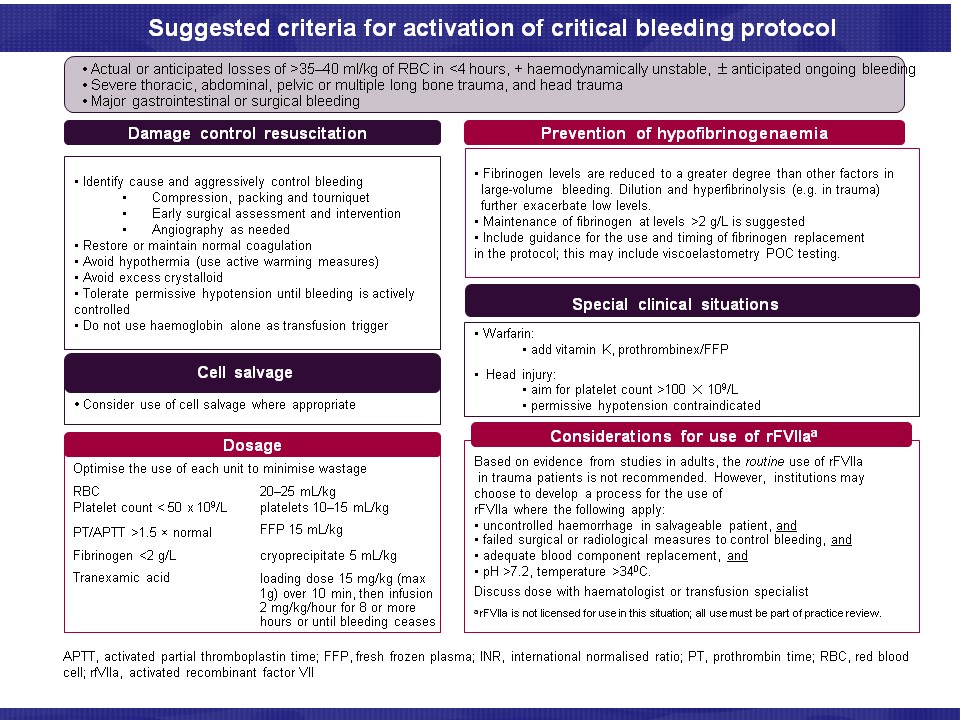
Transfusion volume (mL) = patient’s weight × (desired Hb – patient’s Hb) × transfusion factor

Based on the typical Hct for Australian RBCs (see above), and assuming EBV = 70 mL/kg the ‘transfusion factor’ should be 5. This is in keeping with studies showing that factors of 3 and 4 are insufficient to achieve the desired Hb increment, and that a factor of 4.8 or 5.02 is more appropriate.[400-401](#_ENREF_400)

A transfusion of 10 mL/kg will increase Hb by approximately 20 g/L.

# Appendix K Critical bleeding protocol





# References

1 National Blood Authority (NBA) (2011). *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*, NBA, Canberra, Australia. <http://www.blood.gov.au/pbm-module-1>

2 National Blood Authority (NBA) (2012). *Patient Blood Management Guidelines: Module 2 – Perioperative*, NBA, Canberra, Australia. <http://www.blood.gov.au/pbm-module-2>

3 National Blood Authority (NBA) (2012). *Patient Blood Management Guidelines: Module 3 – Medical*, NBA, Canberra, Australia. <http://www.blood.gov.au/pbm-module-3>

4 National Blood Authority (NBA) (2013). *Patient Blood Management Guidelines: Module 4 – Critical Care*, NBA, Canberra, Australia. <http://www.blood.gov.au/pbm-module-4>

5 National Blood Authority (NBA) (2015). *Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity*, NBA, Canberra, Australia. <http://www.blood.gov.au/pbm-module-5>

6 National Health and Medical Research Council (NHMRC) and Australasian Society of Blood Transfusion (ASBT) (2001). *Clinical practice guidelines on the use of blood components*, NHMRC, Canberra, Australia. <http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp78.pdf>

7 National Blood Authority (NBA) (In preparation). *Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics: Technical Report Volume 1 – Appendixes*, NBA, Canberra, Australia.

8 National Blood Authority (NBA) (In preparation). *Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics: Technical Report Volume 2 – Annexes*, NBA, Canberra, Australia.

9 Adams RJ, McKie VC, Hsu L, Beatrice F, Vichinsky E, Pegelow C, et al. (1998). Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography, *New England Journal of Medicine* 339(1):5–11. <http://www.nejm.org/doi/pdf/10.1056/NEJM199807023390102>

10 Debaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. (2014). Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia, *New England Journal of Medicine* 371(8):699–710. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1401731>

11 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group (2012). KDIGO Clinical practice guideline for anemia in chronic kidney disease, *Kidney Int* 2(4):279–335. <http://kdigo.org/home/guidelines/anemia-in-ckd/>

12 (2015). *Anaemia management in people with chronic kidney disease*, National Institute for Health and Care Excellence (NICE), UK. <http://www.nice.org.uk/guidance/ng8/resources/anaemia-management-in-people-with-chronic-kidney-disease-51046844101>

13 Domellof M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, et al. (2014). Iron requirements of infants and toddlers, *J Pediatr Gastroenterol Nutr* 58(1):119–129. <http://www.ncbi.nlm.nih.gov/pubmed/24135983>

14 Pottie K, Greenaway C, Feightner J, Welch V, Swinkels H, Rashid M, et al. (2011). Evidence-based clinical guidelines for immigrants and refugees, *CMAJ* 183(12):E824–925. <http://www.ncbi.nlm.nih.gov/pubmed/20530168>

15 Baker RI, Coughlin PB, Gallus AS, Harper PL, Salem HH, Wood EM, et al. (2004). Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis, *The Medical Journal of Australia* 181(9):492–497. <https://www.mja.com.au/system/files/issues/181_09_011104/bak10441_fm.pdf>

16 O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, et al. (2004). Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant, *Br J Haematol* 126(1):11-28. <http://www.ncbi.nlm.nih.gov/pubmed/15198728>

17 Treleaven J, Gennery A, Marsh J, Norfolk D, Page L, Parker A, et al. (2011). Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force, *Br J Haematol* 152(1):35–51. <http://onlinelibrary.wiley.com/store/10.1111/j.1365-2141.2010.08444.x/asset/j.1365-2141.2010.08444.x.pdf?v=1&t=i6718wmk&s=e835b22ab47f0481e338307fd908768947388726>

18 Australian & New Zealand Society of Blood Transfusion (ANZSBT) (2011). *Prevention of transfusion-associated graft-versus-host disease (TA-GVHD)*, ANZBST. <http://www.anzsbt.org.au/publications/index.cfm#societyg>

19 McDonald SJ, Middleton P, Dowswell T and Morris PS (2013). Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes, *Cochrane Database Syst Rev* 7:CD004074. <http://www.ncbi.nlm.nih.gov/pubmed/23843134>

20 (2012). *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second edition*, Standing Council on Health. <http://www.blood.gov.au/pubs/ivig/conditions-for-which-IVIg-has-an-emerging-therapeutic-role.html#cdn-09>

21 Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS, et al. (2013). An update of consensus guidelines for warfarin reversal, *The Medical Journal of Australia* 198(4):198–199. <https://www.mja.com.au/system/files/issues/tra10614_web_fm_0.pdf>

22 National Health and Medical Research Council (NHMRC) (2000). *How to use the evidence: assessment and application of scientific evidence*, NHMRC handbook series, NHMRC, Canberra, Australia. <http://www.nhmrc.gov.au/publications/synopses/cp69syn.htm>

23 National Health and Medical Research Council (NHMRC) (2011). *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines*, NHMRC, Canberra, Australia. <http://www.nhmrc.gov.au/guidelines/publications/cp133-and-cp133a>

24 National Health and Medical Research Council (NHMRC) (2009). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*, NHMRC, Canberra, Australia. <http://www.nhmrc.gov.au/guidelines/consult/consultations/add_levels_grades_dev_guidelines2.htm>

25 WFH (2012). *Guidelines for the management of hemophilia (2nd edition)*, World Federation of Hemophilia (WFH). <http://www1.wfh.org/publication/files/pdf-1472.pdf>

26 Aquino D, Marley JV, Senior K, Leonard D, Helmer J, Joshua A, et al. (2013). *Early Childhood Nutrition and Anaemia Prevention Project: Executive summary*, The Fred Hollows Foundation, Indigenous Australia Program, Darwin. <http://www.kamsc.org.au/research/downloads/ECNAPP_Exec_Summary_for_web.pdf>

27 Bar-Zeeve SJ, Kruske SG, Barclay LM, Bar-Zeev N and Kildea SV (2013). Adherence to management guidelines for growth faltering and anaemia in remote dwelling Australian Aboriginal infants and barriers to health service delivery, *BMC Health Services Research* 13(250):1–12. <http://www.biomedcentral.com/content/pdf/1472-6963-13-250.pdf>

28 Brewster DR (2004). Iron deficiency in minority groups in Australia, *J Paediatr Child Health* 40(8):422–423. <http://www.ncbi.nlm.nih.gov/pubmed/15265180>

29 Ciacci C, Sabbatini F, Cavallaro R, Castiglione F, Di Bella S, Iovino P, et al. (2004). Helicobacter pylori impairs iron absorption in infected individuals, *Digestive and Liver Disease* 36(7):455–460. <http://www.dldjournalonline.com/article/S1590-8658(04)00126-4/abstract>

30 Hopkins RM, Gracey MS, Hobbs RP, Spargo RM, Yates M and Thompson RCA (1997). The prevalence of hookworm infection, iron deficiency and anaemia in an aboriginal community in north-west Australia, 166(5):241–244.

31 Kirpalani H and Zupancic JAF (2012). Do transfusions cause necrotizing enterocolitis? The complementary role of randomized trials and observational studies, *Seminars in Perinatology* 36(4):269–276. <http://www.seminperinat.com/article/S0146-0005(12)00029-8/abstract>

32 Mohamed A and Shah PS (2012). Transfusion associated necrotizing enterocolitis: A meta-analysis of observational data, *Pediatrics* 129(3):529–540. <http://pediatrics.aappublications.org/content/129/3/529.full.pdf>

33 AlFaleh K, Al-Jebreen A, Baqays A, Al-Hallali A, Bedaiwi K, Al-Balahi N, et al. (2014). Association of packed red blood cell transfusion and necrotizing enterocolitis in very low birth weight infants, *J Neonatal Perinatal Med* 7(3):193–198. <http://www.ncbi.nlm.nih.gov/pubmed/25318632>

34 Baer VL, Lambert DK, Henry E, Snow GL, Butler A and Christensen RD (2011). Among very-low-birth-weight neonates is red blood cell transfusion an independent risk factor for subsequently developing a severe intraventricular hemorrhage?, *Transfusion* 51(6):1170–1178. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2010.02980.x/abstract>

35 Demirel G, Celik IH, Aksoy HT, Erdeve O, Oguz SS, Uras N, et al. (2012). Transfusion-associated necrotising enterocolitis in very low birth weight premature infants, *Transfusion Medicine* 22(5):332–337. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3148.2012.01170.x/abstract>

36 Dos Santos AMN, Guinsburg R, De Almeida MFB, Procianoy RS, Leone CR, Marba STM, et al. (2011). Red blood cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants, *Journal of Pediatrics* 159(3):371–376. <http://www.sciencedirect.com/science/article/pii/S0022347611002459>

37 Elabiad MT, Harsono M, Talati AJ and Dhanireddy R (2013). Effect of birth weight on the association between necrotising enterocolitis and red blood cell transfusions in (less-than or equal to)1500 g infants, *BMJ Open* 3(11). <http://dx.doi.org/10.1136/bmjopen-2013-003823>

38 Feghhi M, Altayeb SMH, Haghi F, Kasiri A, Farahi F, Dehdashtyan M, et al. (2012). Incidence of retinopathy of prematurity and risk factors in the South-Western Region of Iran, *Middle East African Journal of Ophthalmology* 19(1):101–106. <http://www.meajo.org/article.asp?issn=0974-9233;year=2012;volume=19;issue=1;spage=101;epage=106;aulast=Feghhi>

39 Fortes Filho JB, Borges Fortes BG, Tartarella MB and Procianoy RS (2013). Incidence and main risk factors for severe retinopathy of prematurity in infants weighing less than 1000 grams in Brazil, *Journal of Tropical Pediatrics* 59(6):502–506. <http://dx.doi.org/10.1093/tropej/fmt036>

40 Hakeem A, Mohamed GB and Othman MF (2012). Retinopathy of prematurity: A study of incidence and risk factors in nicu of al-minya university hospital in egypt, *Journal of Clinical Neonatology* 1(2):76–81. <http://dx.doi.org/10.4103/2249-4847.96755>

41 Kabatas EU, Beken S, Aydin B, Dilli D, Zenciroglu A and Okumus N (2013). The risk factors for retinopathy of prematurity and need of laser photocoagulation: A single center experience, *Gazi Medical Journal* 24(4). <http://dx.doi.org/10.12996/gmj.2013.31>

42 Li ML, Hsu SM, Chang YS, Shih MH, Lin YC, Lin CH, et al. (2013). Retinopathy of prematurity in southern Taiwan: A 10-year tertiary medical center study, *Journal of the Formosan Medical Association* 112(8):445–453. <http://www.jfma-online.com/article/S0929-6646(12)00236-7/pdf>

43 Navaei F, Aliabady B, Moghtaderi J, Moghtaderi M and Kelishadi R (2010). Early outcome of preterm infants with birth weight of 1500 g or less and gestational age of 30 weeks or less in Isfahan city, Iran, *World J Pediatr* 6(3):228-232. <http://www.ncbi.nlm.nih.gov/pubmed/20549417>

44 Stritzke AI, Smyth J, Synnes A, Lee SK and Shah PS (2013). Transfusion-associated necrotising enterocolitis in neonates, *Archives of Disease in Childhood: Fetal and Neonatal Edition* 98(1):F10–F14. <http://fn.bmj.com/content/98/1/F10.long>

45 Wan-Huen P, Bateman D, Shapiro DM and Parravicini E (2013). Packed red blood cell transfusion is an independent risk factor for necrotizing enterocolitis in premature infants, *Journal of Perinatology* 33(10):786–790. <http://dx.doi.org/10.1038/jp.2013.60>

46 Weintraub Z, Carmi N, Elouti H and Rumelt S (2011). The association between stage 3 or higher retinopathy of prematurity and other disorders of prematurity, *Canadian Journal of Ophthalmology* 46(5):419–424. <http://www.canadianjournalofophthalmology.ca/article/S0008-4182(11)00166-9/abstract>

47 Bassler D, Weitz M, Bialkowski A and Poets CF (2008). Restrictive versus liberal red blood cell transfusion strategies for preterm infants: A systematic review of randomized controlled trials, *Current Pediatric Reviews* 4(3):143–150. <http://dx.doi.org/10.2174/157339608785855983>

48 Ibrahim M, Ho SKY and Yeo CL (2014). Restrictive versus liberal red blood cell transfusion thresholds in very low birth weight infants: A systematic review and meta-analysis, *Journal of Paediatrics and Child Health* 50(2):122–130. <http://dx.doi.org/10.1111/jpc.12409>

49 Venkatesh V, Khan R, Curley A, Hopewell S, Doree C and Stanworth S (2012). The safety and efficacy of red cell transfusions in neonates: A systematic review of randomized controlled trials, *Br J Haematol* 158(3):370–385. <http://onlinelibrary.wiley.com/store/10.1111/j.1365-2141.2012.09180.x/asset/bjh9180.pdf?v=1&t=i7cjieyn&s=7bd53943fb622f00991723d31ed63825d6438702>

50 Whyte R and Kirpalani H (2011). Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants, *Cochrane database of systematic reviews (Online)* (11):CD000512. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L560067527>

51 Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, et al. (2005). Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants, *Pediatrics* 115(6):1685–1691. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2866196/pdf/nihms-199759.pdf>

52 Chen HL, Tseng HI, Lu CC, Yang SN, Fan HC and Yang RC (2009). Effect of Blood Transfusions on the Outcome of Very Low Body Weight Preterm Infants under Two Different Transfusion Criteria, *Pediatrics and Neonatology* 50(3):110–116. <http://www.pediatr-neonatol.com/article/S1875-9572(09)60045-0/pdf>

53 Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, et al. (2006). The premature infants in need of transfusion (pint) study: A randomized, controlled trial of a restrictive (LOW) versus liberal (HIGH) transfusion threshold for extremely low birth weight infants, *Journal of Pediatrics* 149(3):301–307. <http://www.jpeds.com/article/S0022-3476(06)00444-6/abstract>

54 Brooks SE, Marcus DM, Gillis D, Pirie E, Johnson MH and Bhatia J (1999). The effect of blood transfusion protocol on retinopathy of prematurity: A prospective, randomized study, *Pediatrics* 104(3 I):514–518. <http://dx.doi.org/10.1542/peds.104.3.514>

55 Connelly RJ, Stone SH and Whyte RK (1998). Early vs. late red cell transfusion in low birth weight infants, *Pediatr Res* 43(4):170A.

56 Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, et al. (2009). Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion, *Pediatrics* 123(1):207–213. <http://pediatrics.aappublications.org/content/123/1/207.long>

57 Boost Ii United Kingdom Collaborative Group, Boost Ii Australia Collaborative Group, Boost Ii New Zealand Collaborative Group, Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. (2013). Oxygen saturation and outcomes in preterm infants, *N Engl J Med* 368(22):2094–2104. <http://www.ncbi.nlm.nih.gov/pubmed/23642047>

58 Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. (2012). Red blood cell transfusion: a clinical practice guideline from the AABB, *Annals of Internal Medicine* 157(1):49–58. <http://annals.org/data/Journals/AIM/24329/0000605-201207030-00008.pdf>

59 Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. (2007). Transfusion strategies for patients in pediatric intensive care units, *New England Journal of Medicine* 356(16):1609–1619. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa066240>

60 *TCD With Transfusions Changing to Hydroxyurea (TWiTCH): A Phase III Randomized Clinical Trial to Compare Standard Therapy (Erythrocyte Transfusions) With Alternative Therapy (Hydroxyurea) for the Maintenance of Lowered TCD Velocities in Pediatric Subjects With Sickle Cell Anemia and Abnormal Pre-treatment TCD Velocities*. <https://clinicaltrials.gov/ct2/show/study/NCT01425307?term=Twitch+sickle+cell&rank=1>

61 Bernaudin M, Bellail A, Marti HH, Yvon A, Vivien D, Duchatelle I, et al. (2000). Neurons and astrocytes express EPO mRNA: oxygen-sensing mechanisms that involve the redox-state of the brain, *Glia* 30(3):271–278. <http://www.ncbi.nlm.nih.gov/pubmed/10756076>

62 Pegelow CH, Macklin EA, Moser FG, Wang WC, Bello JA, Miller ST, et al. (2002). Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease, *Blood* 99(8):3014–3018. <http://www.ncbi.nlm.nih.gov/pubmed/11929794>

63 Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y, et al. (2012). The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: A Systematic Review and Economic Evaluation, *Health Technology Assessment* 16(43):1–129. <http://dx.doi.org/10.3310/hta16430>

64 Wang WC and Dwan K (2013). Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease, *Cochrane Database of Systematic Reviews*.

65 Adams RJ and Brambilla D (2005). Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease, *New England Journal of Medicine* 353(26):2769–2778. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa050460>

66 Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, et al. (2001). Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity, *Archives of Neurology* 58(12):2017–2021. <http://archneur.jamanetwork.com/data/Journals/NEUR/6833/NOC10072.pdf>

67 US Department of Health and Human Services and National Institutes of Health (NIH) (2014). *Evidence-based management of sickle cell disease: Expert panel report*, Bethesda, USA. <https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines>

68 Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y and De Stefano P (1997). A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis, *Transfusion* 37(2):135–140. <http://www.ncbi.nlm.nih.gov/pubmed/9051086>

69 Masera G, Terzoli S, Avanzini A, Fontanelli G, Mauri RA, Piacentini G, et al. (1982). Evaluation of the supertransfusion regimen in homozygous beta-thalassaemia children, *Br J Haematol* 52(1):111–113. <http://www.ncbi.nlm.nih.gov/pubmed/7115620>

70 Torcharus K, Withayathawornwong W, Sriphaisal T, Krutvacho T, Arnutti P and Suwanasophorn C (1993). High transfusion in children with beta-thalassemia/Hb E: clinical and laboratory assessment of 18 cases, *Southeast Asian J Trop Med Public Health* 24 Suppl 1:96–99. <http://www.ncbi.nlm.nih.gov/pubmed/7886617>

71 Jaime-Perez JC, Colunga-Pedraza PR and Gomez-Almaguer D (2011). Is the number of blood products transfused associated with lower survival in children with acute lymphoblastic leukemia?, *Pediatric Blood and Cancer* 57(2):217–223. <http://dx.doi.org/10.1002/pbc.22957>

72 Kneyber MCJ, Grotenhuis F, Berger RFM, Ebels TW, Burgerhof JGM and Albers MJIJ (2013). Transfusion of leukocyte-depleted RBCs is independently associated with increased morbidity after pediatric cardiac surgery, *Pediatric Critical Care Medicine* 14(3):298–305. <http://dx.doi.org/10.1097/PCC.0b013e3182745472>

73 Nacoti M, Cazzaniga S, Lorusso F, Naldi L, Brambillasca P, Benigni A, et al. (2012). The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation, *Pediatric Transplantation* 16(4):357–366. <http://www.ncbi.nlm.nih.gov/pubmed/22429563>

74 Redlin M, Kukucka M, Boettcher W, Schoenfeld H, Huebler M, Kuppe H, et al. (2013). Blood transfusion determines postoperative morbidity in pediatric cardiac surgery applying a comprehensive blood-sparing approach, *Journal of Thoracic and Cardiovascular Surgery* 146(3):537–542. <http://www.jtcvsonline.org/article/S0022-5223(12)01432-8/abstract>

75 Wilkinson KL, Brunskill SJ, Doree C, Trivella M, Gill R and Murphy MF (2014). Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease, *Cochrane Database of Systematic Reviews*.

76 Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M and Lerner NB (2011). Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy, *Pediatric Critical Care Medicine* 12(1):39–45. <http://dx.doi.org/10.1097/PCC.0b013e3181e329db>

77 Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, et al. (2010). Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis, *Critical Care Medicine* 38(2):649–656. <http://dx.doi.org/10.1097/CCM.0b013e3181bc816c>

78 Rouette J, Trottier H, Ducruet T, Beaunoyer M, Lacroix J and Tucci M (2010). Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: A randomized clinical trial, *Annals of Surgery* 251(3):421–427. <http://dx.doi.org/10.1097/SLA.0b013e3181c5dc2e>

79 Robitaille N, Lacroix J, Alexandrov L, Clayton L, Cortier M, Schultz KR, et al. (2013). Excess of Veno-Occlusive Disease in a Randomized Clinical Trial on a Higher Trigger for Red Blood Cell Transfusion after Bone Marrow Transplantation: A Canadian Blood and Marrow Transplant Group Trial, *Biology of Blood and Marrow Transplantation* 19(3):468–473. <http://www.bbmt.org/article/S1083-8791(12)01138-X/pdf>

80 Acker SN, Partrick DA, Ross JT, Nadlonek NA, Bronsert M and Bensard DD (2014). Blood component transfusion increases the risk of death in children with traumatic brain injury, *Journal of Trauma and Acute Care Surgery* 76(4):1082–1088. <http://dx.doi.org/10.1097/TA.0000000000000095>

81 Fremgen HE, Bratton SL, Metzger RR and Barnhart DC (2014). Pediatric liver lacerations and intensive care: Evaluation of ICU triage strategies, *Pediatric Critical Care Medicine* 15(4):e183–e191. <http://dx.doi.org/10.1097/PCC.0000000000000102>

82 Hassan NE, DeCou JM, Reischman D, Nickoles TA, Gleason E, Ropele DL, et al. (2014). RBC transfusions in children requiring intensive care admission after traumatic injury, *Pediatric Critical Care Medicine*. <http://dx.doi.org/10.1097/PCC.0000000000000192>

83 Carson JL, Carless PA and Hebert PC (2012). Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion, *Cochrane Database of Systematic Reviews* (4). <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002042.pub3/pdf>

84 Desjardins P, Turgeon AF, Tremblay MH, Lauzier F, Zarychanski R, Boutin A, et al. (2012). Hemoglobin levels and transfusions in neurocritically ill patients: A systematic review of comparative studies, *Crit Care* 16(2). <http://dx.doi.org/10.1186/cc11293>

85 Aher SM and Ohlsson A (2012). Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants, *Cochrane database of systematic reviews (Online)* 9:CD004868. <http://onlinelibrary.wiley.com/store/10.1002/14651858.CD004868.pub3/asset/CD004868.pdf?v=1&t=i7cj6vg7&s=087822d8d9761f683303b3217245e028201185f4>

86 Garcia MG, Hutson AD and Christensen RD (2002). Effect of recombinant erythropoietin on "late" transfusions in the neonatal intensive care unit: A meta-analysis, *Journal of Perinatology* 22(2):108–111. <http://www.nature.com/jp/journal/v22/n2/pdf/7210677a.pdf>

87 Kotto-Kome AC, Garcia MG, Calhoun DA and Christensen RD (2004). Effect of beginning recombinant erythropoietin treatment within the first week of life, among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: A meta-analysis, *Journal of Perinatology* 24(1):24–29. <http://www.nature.com/jp/journal/v24/n1/pdf/7211018a.pdf>

88 Ohlsson A and Aher SM (2012). Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants, *Cochrane database of systematic reviews (Online)* 9:CD004863. <http://onlinelibrary.wiley.com/store/10.1002/14651858.CD004863.pub3/asset/CD004863.pdf?v=1&t=i7cj8hx8&s=942e4e221b6e730c654041e1f6f94411f1d6e01b>

89 Vamvakas EC and Strauss RG (2001). Meta-analysis of controlled clinical trials studying the efficacy of rHuEPO in reducing blood transfusions in the anemia of prematurity, *Transfusion* 41(3):406–415. <http://onlinelibrary.wiley.com/doi/10.1046/j.1537-2995.2001.41030406.x/abstract>

90 Xu XJ, Huang HY and Chen HL (2014). Erythropoietin and retinopathy of prematurity: a meta-analysis, *European Journal of Pediatrics*. <http://dx.doi.org/10.1007/s00431-014-2332-4>

91 El-Ganzoury MM, Awad HA, El-Farrash RA, El-Gammasy TM, Ismail EA, Mohamed HE, et al. (2014). Enteral Granulocyte-Colony Stimulating Factor and Erythropoietin Early in Life Improves Feeding Tolerance in Preterm Infants: A Randomized Controlled Trial, *Journal of Pediatrics*. <http://dx.doi.org/10.1016/j.jpeds.2014.07.034>

92 Jim WT, Chen LT, Huang FY and Shu CH (2000). The early use of recombinant human erythropoietin in anemia of prematurity, *Clinical Neonatology* 7(2):12–16. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L47248848>

93 Kremenopoulos G, Soubasi V, Tsantali C, Diamanti E and Tsakiris D (1997). The best timing of recombinant human erythropoietin administration in anemia of prematurity: A randomized controlled study, *International Journal of Pediatric Hematology/Oncology* 4(4):373–383. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L27501001>

94 Ovali F, Samanci N and Dagoglu T (1996). Management of late anemia in rhesus hemolytic disease: Use of recombinant human erythropoietin (a pilot study), *Pediatr Res* 39(5):831–834.

95 Aher SM and Ohlsson A (2014). Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants, *Cochrane Database Syst Rev* 4:CD004868. <http://www.ncbi.nlm.nih.gov/pubmed/24760628>

96 Ohlsson A and Aher SM (2014). Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants, *Cochrane Database Syst Rev* 4:CD004863. <http://www.ncbi.nlm.nih.gov/pubmed/24771408>

97 Collard KJ (2009). Iron homeostasis in the neonate, *Pediatrics* 123(4):1208-1216. <http://www.ncbi.nlm.nih.gov/pubmed/19336381>

98 Friel JK, Andrews WL, Aziz K, Kwa PG, Lepage G and L'Abbe MR (2001). A randomized trial of two levels of iron supplementation and developmental outcome in low birth weight infants, *J Pediatr* 139(2):254-260. <http://www.ncbi.nlm.nih.gov/pubmed/11487753>

99 Long H, Yi JM, Hu PL, Li ZB, Qiu WY, Wang F, et al. (2012). Benefits of iron supplementation for low birth weight infants: a systematic review, *BMC Pediatr* 12:99. <http://www.ncbi.nlm.nih.gov/pubmed/22794149>

100 Taylor TA and Kennedy KA (2013). Randomized trial of iron supplementation versus routine iron intake in VLBW infants, *Pediatrics* 131(2):e433–e438. <http://pediatrics.aappublications.org/content/131/2/e433.full.pdf>

101 Sankar MJ, Saxena R, Mani K, Agarwal R, Deorari AK and Paul VK (2009). Early iron supplementation in very low birth weight infants - A randomized controlled trial, *Acta Paediatrica, International Journal of Paediatrics* 98(6):953–958. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354556418>

102 Berseth CL, Van Aerde JE, Gross S, Stolz SI, Harris CL and Hansen JW (2004). Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier, *Pediatrics* 114(6):e699–706. <http://www.ncbi.nlm.nih.gov/pubmed/15545616>

103 Franz AR, Mihatsch WA, Sander S, Kron M and Pohlandt F (2000). Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams, *Pediatrics* 106(4):700–706. <http://www.ncbi.nlm.nih.gov/pubmed/11015511>

104 Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. (2010). Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition, *J Pediatr Gastroenterol Nutr* 50(1):85–91. <http://www.ncbi.nlm.nih.gov/pubmed/19881390>

105 Kleinman R and Greer F (Eds.) (2014). *Pediatric Nutrition Handbook, 7th edition,* American Academy of Pediatrics Committee on Nutrition, Elk Grove Village, IL.

106 Pasricha SR, Hayes E, Kalumba K and Biggs BA (2013). Effect of daily iron supplementation on health in children aged 4-23 months: A systematic review and meta-analysis of randomised controlled trials, *The Lancet Global Health* 1(2):e77–e86. <http://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X(13)70046-9.pdf>

107 Okebe JU, Yahav D, Shbita R and Paul M (2011). Oral iron supplements for children in malaria-endemic areas, *Cochrane database of systematic reviews (Online)* (10):CD006589. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L362839424>

108 Feusner J and Hastings C (2002). Recombinant human erythropoietin in pediatric oncology: a review (Structured abstract), *Medical and Pediatric Oncology* 39:463–468. <http://onlinelibrary.wiley.com/doi/10.1002/mpo.10187/abstract>

109 Grant MD, Piper M, Bohlius J, Tonia T, Robert N, Vats V, et al. (2013). *Epoetin and darbepoetin formanaging anemia in patients undergoing cancer treatment: comparative effectiveness update*, Comparative Effectiveness Review No. 113, Agency for Healthcare Research and Quality, Rockville, MD.

110 Mystakidou K, Potamianou A and Tsilika E (2007). Erythropoietic growth factors for children with cancer: A systematic review of the literature, *Current Medical Research and Opinion* 23(11):2841–2847. <http://informahealthcare.com/doi/abs/10.1185/030079907X242601%20>

111 Ross SD, Allen IE, Henry DH, Seaman C, Sercus B and Goodnough LT (2006). Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature (Structured abstract), *Clinical Therapeutics* 28:801–831. <http://www.clinicaltherapeutics.com/article/S0149-2918(06)00139-1/abstract>

112 Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. (2012). Erythropoietin or darbepoetin for patients with cancer, *Cochrane Database of Systematic Reviews* (12). <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003407.pub5/pdf>

113 Bennetts G, Bertolone S, Bray G and al. e (1995). Erythropoietin reduces volume of red cell transfusions required in some subsets of children with acute lymphocytic leukemia [abstract], *Blood* 10:853.

114 Csaki C, Ferencz T, Schuler D and Borsi J (1998). Recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia in children with malignant solid tumours, *European Journal of Cancer* 34(3):364–367. <http://www.sciencedirect.com/science/article/pii/S095980499710065X>

115 Porter JC, Leahey A, Polise K, Bunin G and Manno CS (1996). Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: a randomized, double-blind, placebo-controlled trial, *J Pediatr* 129(5):656–660. <http://www.ncbi.nlm.nih.gov/pubmed/8917229>

116 Ragni G, Clerico A, Sordi A and al. e (1998). Recombinant human erythropoietin (rHuEPO) in children with cancer: A randomized study [abstract], *Med Pediatr Oncol* 31:274.

117 Razzouk BI, Hord JD, Hockenberry M, Hinds PS, Feusner J, Williams D, et al. (2006). Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy, *J Clin Oncol* 24(22):3583–3589. <http://www.ncbi.nlm.nih.gov/pubmed/16877725>

118 Varan A, Büyükpamukçu M, Kutluk T and Akyüz C (1999). Recombinant human erythropoietin treatment for chemotherapy-related anemia in children, *Pediatrics* 103(2):e16–e16. <http://pediatrics.aappublications.org/content/103/2/e16.short>

119 Wagner LM, Billups CA, Furman WL, Rao BN and Santana VM (2004). Combined use of erythropoietin and granulocyte colony-stimulating factor does not decrease blood transfusion requirements during induction therapy for high-risk neuroblastoma: a randomized controlled trial, *Journal of clinical oncology* 22(10):1886–1893. <http://jco.ascopubs.org/content/22/10/1886.short>

120 (2011). *Anaemia management in people with chronic kidney disease*, National Institute for Health and Care Excellence (NICE), UK. <http://www.nice.org.uk/guidance/cg114>

121 Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, et al. (2005). Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients, *Cochrane Database Syst Rev* (3):CD003266. <http://www.ncbi.nlm.nih.gov/pubmed/16034896>

122 Pape L, Ahlenstiel T, Kreuzer M, Drube J, Froede K, Franke D, et al. (2009). Early erythropoietin reduced the need for red blood cell transfusion in childhood hemolytic uremic syndrome - A randomized prospective pilot trial, *Pediatric Nephrology* 24(5):1061–1064. <http://link.springer.com/article/10.1007%2Fs00467-008-1087-4>

123 Albaramki J, Hodson EM, Craig JC and Webster AC (2012). Parenteral versus oral iron therapy for adults and children with chronic kidney disease, *Cochrane Database Syst Rev* 1:CD007857. <http://www.ncbi.nlm.nih.gov/pubmed/22258974>

124 Warady BA, Kausz A, Lerner G, Brewer ED, Chadha V, Brugnara C, et al. (2004). Iron therapy in the pediatric hemodialysis population, *Pediatric Nephrology* 19(6):655–661. <http://link.springer.com/article/10.1007%2Fs00467-004-1457-5>

125 Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. (2010). The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS), *Blood* 115(12):2354-2363. <http://www.ncbi.nlm.nih.gov/pubmed/19903897>

126 Jones AP, Davies S and Olujohungbe A (2001). Hydroxyurea for sickle cell disease, *Cochrane Database Syst Rev* (2):CD002202. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002202/epdf>

127 Mulaku M, Opiyo N, Karumbi J, Kitonyi G, Thoithi G and English M (2013). Evidence review of hydroxyurea for the prevention of sickle cell complications in low-income countries, *Archives of Disease in Childhood* 98(11):908–914. <http://adc.bmj.com/content/98/11/908.full.pdf>

128 Segal JB, Strouse JJ, Beach MC, Haywood C, Witkop C, Park H, et al. (2008). Hydroxyurea for the treatment of sickle cell disease, *Evid Rep Technol Assess (Full Rep)* (165):1-95. <http://www.ncbi.nlm.nih.gov/pubmed/18457478>

129 Jain DL, Sarathi V, Desai S, Bhatnagar M and Lodha A (2012). Low fixed-dose hydroxyurea in severely affected Indian children with sickle cell disease, *Hemoglobin* 36(4):323–332. <http://informahealthcare.com/doi/abs/10.3109/03630269.2012.697948>

130 Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. (2011). Hydroxycarbamide in very young children with sickle-cell anaemia: A multicentre, randomised, controlled trial (BABY HUG), *The Lancet* 377(9778):1663–1672. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3133619/pdf/nihms298546.pdf>

131 Andropoulos DB, Brady K, Easley RB, Dickerson HA, Voigt RG, Shekerdemian LS, et al. (2013). Erythropoietin neuroprotection in neonatal cardiac surgery: A phase I/II safety and efficacy trial, *Journal of Thoracic and Cardiovascular Surgery* 146(1):124–131. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579008/pdf/nihms417782.pdf>

132 Bierer R, Roohi M, Peceny C and Ohls RK (2009). Erythropoietin increases reticulocyte counts and maintains hematocrit in neonates requiring surgery, *Journal of Pediatric Surgery* 44(8):1540–1545. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086684/pdf/nihms281836.pdf>

133 Fearon JA and Weinthal J (2002). The use of recombinant erythropoietin in the reduction of blood transfusion rates in craniosynostosis repair in infants and children, *Plastic and Reconstructive Surgery* 109(7):2190–2196. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L34556189>

134 Chicella MF and Krueger KP (2006). Prospective randomized double-blind placebo controlled trial of recombinant human erythropoietin administration to reduce blood transfusions in anemic pediatric intensive care patients, *The Journal of Pediatric Pharmacology and Therapeutics* 11(2):101–106. <http://www.jppt.org/doi/abs/10.5863/1551-6776-11.2.101>

135 Jacobs BR, Lyons K and Brilli RJ (2003). Erythropoietin therapy in children with bronchiolitis and anemia, *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 4(1):44–48. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36652247>

136 Osborn DA and Evans N (2004). Early volume expansion for prevention of morbidity and mortality in very preterm infants, *Cochrane database of systematic reviews (Online)* (2):CD002055. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39041654>

137 The Northern Neonatal Nursing Initiative Trial G (1996a). A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or gluocse on early mortality and morbidity in preterm babies, *Eur J Pediatr* 155:580–588.

138 The Northern Neonatal Nursing Initiative Trial Group (1996b). Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years, *The Lancet* 348:229–232.

139 Baer VL, Lambert DK, Henry E, Snow GL, Sola-Visner MC and Christensen RD (2007). Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopenic neonates in a multihospital healthcare system, *Journal of Perinatology* 27(12):790–796. <http://www.ncbi.nlm.nih.gov/pubmed/17855804>

140 Bonifacio L, Petrova A, Nanjundaswamy S and Mehta R (2007). Thrombocytopenia related neonatal outcome in preterms, *Indian Journal of Pediatrics* 74(3):267–274. <http://www.ncbi.nlm.nih.gov/pubmed/17401266>

141 Christensen RD, Henry E, Wiedmeier SE, Stoddard RA, Sola-Visner MC, Lambert DK, et al. (2006). Thrombocytopenia among extremely low birth weight neonates: Data from a multihospital healthcare system, *Journal of Perinatology* 26(6):348–353. <http://www.ncbi.nlm.nih.gov/pubmed/16642027>

142 Von Lindern JS, Hulzebos CV, Bos AF, Brand A, Walther FJ and Lopriore E (2012). Thrombocytopaenia and intraventricular haemorrhage in very premature infants: A tale of two cities, *Arch Dis Child Fetal Neonatal Ed* 97(5):F348–352. <http://fn.bmj.com/content/97/5/F348.long>

143 Curley A, Venkatesh V, Stanworth S, Clarke P, Watts T, New H, et al. (2014). Platelets for neonatal transfusion - study 2: a randomised controlled trial to compare two different platelet count thresholds for prophylactic platelet transfusion to preterm neonates, *Neonatology* 106(2):102-106. <http://www.ncbi.nlm.nih.gov/pubmed/24851997>

144 Estcourt L, Stanworth S, Doree C, Hopewell S, Murphy MF, Tinmouth A, et al. (2012). Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation, *Cochrane Database of Systematic Reviews* 16(5). <http://www.ncbi.nlm.nih.gov/pubmed/22592695>

145 Roy AJ, Jaffe N and Djerassi I (1973). Prophylactic platelet transfusions in children with acute leukemia: a dose response study, *Transfusion* 13(5):283-290. <http://www.ncbi.nlm.nih.gov/pubmed/4750180>

146 Murphy S, Litwin S, Herring LM, Koch P, Remischovsky J, Donaldson MH, et al. (1982). Indications for platelet transfusion in children with acute leukemia, *Am J Hematol* 12(4):347-356. <http://www.ncbi.nlm.nih.gov/pubmed/6981349>

147 Nahirniak S, Slichter SJ, Tanael S, Rebulla P, Pavenski K, Vassallo R, et al. (2015). Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia, *Transfus Med Rev* 29(1):3-13. <http://www.ncbi.nlm.nih.gov/pubmed/25537844>

148 Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. (2015). Platelet transfusion: a clinical practice guideline from the AABB, *Ann Intern Med* 162(3):205-213. <http://www.ncbi.nlm.nih.gov/pubmed/25383671>

149 Lee JW, Yoo YC, Park HK, Bang SO, Lee KY and Bai SJ (2013). Fresh frozen plasma in pump priming for congenital heart surgery: Evaluation of effects on postoperative coagulation profiles using a fibrinogen assay and rotational thromboelastometry, *Yonsei Medical Journal* 54(3):752–762. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3635629/pdf/ymj-54-752.pdf>

150 McCall MM, Blackwell MM, Smyre JT, Sistino JJ, Acsell JR, Dorman BH, et al. (2004). Fresh frozen plasma in the pediatric pump prime: A prospective, randomized trial, *Annals of Thoracic Surgery* 77(3):983–987. <http://www.annalsthoracicsurgery.org/article/S0003-4975(03)01873-3/pdf>

151 Oliver, Jr., Beynen FM, Nuttall GA, Schroeder DR, Ereth MH, Dearani JA, et al. (2003). Blood loss in infants and children for open heart operations: Albumin 5% versus fresh-frozen plasma in the prime, *Annals of Thoracic Surgery* 75(5):1506–1512. <http://www.annalsthoracicsurgery.org/article/S0003-4975(02)04991-3/pdf>

152 British Committee for Standards in Haematology BTTF (2003). Guidelines for the use of platelet transfusions, *Br J Haematol* 122(1):10–23. <http://onlinelibrary.wiley.com/store/10.1046/j.1365-2141.2003.04468.x/asset/j.1365-2141.2003.04468.x.pdf?v=1&t=i8wrvhu3&s=cb4be396ff1b4b0096669308ddb29fd06023531e>

153 Lunde J, Stensballe J, Wikkelso A, Johansen M and Afshari A (2014). Fibrinogen concentrate for bleeding--a systematic review, *Acta Anaesthesiol Scand* 58(9):1061-1074. <http://www.ncbi.nlm.nih.gov/pubmed/25059813>

154 Galas FRBG, de Almeida JP, Fukushima JT, Vincent JL, Osawa EA, Zeferino S, et al. (2014). Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: A randomized pilot trial, *Journal of Thoracic and Cardiovascular Surgery*. <http://dx.doi.org/10.1016/j.jtcvs.2014.04.029>

155 Church GD, Matthay MA, Liu K, Milet M and Flori HR (2009). Blood product transfusions and clinical outcomes in pediatric patients with acute lung injury, *Pediatric Critical Care Medicine* 10(3):297–302. <http://www.ncbi.nlm.nih.gov/pubmed/19307809>

156 Karam O, Lacroix J, Robitaille N, Rimensberger PC and Tucci M (2013). Association between plasma transfusions and clinical outcome in critically ill children: A prospective observational study, *Vox Sanguinis* 104(4):342–349. <http://onlinelibrary.wiley.com/doi/10.1111/vox.12009/abstract>

157 Vain NE, Satragno DS, Gorenstein AN, Gordillo JE, Berazategui JP, Alda MG, et al. (2014). Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial, *Lancet* 384(9939):235-240. <http://www.ncbi.nlm.nih.gov/pubmed/24746755>

158 Airey RJ, Farrar D and Duley L (2010). Alternative positions for the baby at birth before clamping the umbilical cord, *Cochrane Database Syst Rev* (10):CD007555. <http://www.ncbi.nlm.nih.gov/pubmed/20927760>

159 Backes CH, Rivera BK, Haque U, Bridge JA, Smith CV, Hutchon DJR, et al. (2014). Placental transfusion strategies in very preterm neonates: A systematic review and meta-analysis, *Obstetrics and Gynecology* 124(1):47–56. <http://dx.doi.org/10.1097/AOG.0000000000000324>

160 Ghavam S, Batra D, Mercer J, Kugelman A, Hosono S, Oh W, et al. (2013). Effects of placental transfusion in extremely low birthweight infants: Meta-analysis of long- and short-term outcomes, *Transfusion* 54(4):1192–1198. <http://onlinelibrary.wiley.com/doi/10.1111/trf.12469/abstract>

161 Mathew JL (2011). Timing of umbilical cord clamping in term and preterm deliveries and infant and maternal outcomes: A systematic review of randomized controlled trials, *Indian Pediatrics* 48(2):123–129. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L361595745>

162 Rabe H, Diaz-Rossello JL, Duley L and Dowswell T (2012). Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes, *Cochrane database of systematic reviews (Online)* 8:CD003248. <http://onlinelibrary.wiley.com/store/10.1002/14651858.CD003248.pub3/asset/CD003248.pdf?v=1&t=ib8vzpvn&s=c8dc1f9b1a3381b5fec4e1ebd1ae74974f8cdf2f>

163 Alan S, Arsan S, Okulu E, Akin IM, Kilic A, Taskin S, et al. (2014). Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born (less-than or equal to)1500 g: A prospective, randomized, controlled trial, *J Pediatr Hematol Oncol*. <http://dx.doi.org/10.1097/MPH.0000000000000143>

164 Katheria AC, Leone TA, Woelkers D, Garey DM, Rich W and Finer NN (2014). The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates, *J Pediatr* 164(5):1045–1050.e1041. <http://www.jpeds.com/article/S0022-3476(14)00030-4/abstract>

165 Bowen JR, Patterson JA, Roberts CL, Isbister JP, Irving DO and Ford JB (2015). Red cell and platelet transfusions in neonates: a population-based study, *Arch Dis Child Fetal Neonatal Ed*. <http://www.ncbi.nlm.nih.gov/pubmed/25977265>

166 Hammerman C, Vreman HJ, Kaplan M and Stevenson DK (1996). Intravenous immune globulin in neonatal immune hemolytic disease: does it reduce hemolysis?, *Acta Paediatr* 85(11):1351-1353. <http://www.ncbi.nlm.nih.gov/pubmed/8955465>

167 Louis D, More K, Oberoi S and Shah PS (2014). Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: An updated systematic review and meta-analysis, *Archives of Disease in Childhood: Fetal and Neonatal Edition*. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L53004290>

168 Chitty HE, Ziegler N, Savoia H, Doyle LW and Fox LM (2013). Neonatal exchange transfusions in the 21st century: a single hospital study, *J Paediatr Child Health* 49(10):825-832. <http://www.ncbi.nlm.nih.gov/pubmed/23834341>

169 Liley HG, Gardener G, Lopriore E and Smits-Wintjens V (2015). Immune Hemolytic Disease, In Orkin SH, Nathan DG, et al. (eds.), *Nathan and Oskit's Hematology and Oncology of Infancy and Childhood, 8th Edition*, Elsevier.

170 Caputo M, Patel N, Angelini GD, Siena P, Stoica S, Parry AJ, et al. (2011). Effect of normothermic cardiopulmonary bypass on renal injury in pediatric cardiac surgery: a randomized controlled trial, *J Thorac Cardiovasc Surg* 142:1114–1121, 1121. <http://www.jtcvsonline.org/article/S0022-5223(11)00848-8/pdf>

171 Precious DS, Splinter W and Bosco D (1996). Induced hypotensive anesthesia for adolescent orthognathic surgery patients, *Journal of Oral and Maxillofacial Surgery* 54(6):680–683, discussion 683–684. <http://www.joms.org/article/S0278-2391(96)90679-5/abstract>

172 Friesen RH, Perryman KM, Weigers KR, Mitchell MB and et al. (2006). *A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants*, 16:429–435.

173 Hans P, Collin V, Bonhomme V, Damas F, Born JD and Lamy M (2000). Evaluation of acute normovolemic hemodilution for surgical repair of craniosynostosis, *Journal of Neurosurgical Anesthesiology* 12(1):33–36.

174 Lisander B, Jonsson R and Nordwall A (1996). Combination of blood-saving methods decreases homologous blood requirements in scoliosis surgery, *Anaesthesia and Intensive Care* 24(5):555–558.

175 Cholette JM, Powers KS, Alfieris GM, Angona R, Henrichs KF, Masel D, et al. (2013). Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomized, clinical trial, *Pediatric Critical Care Medicine* 14(2):137–147. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3671922/pdf/nihms463601.pdf>

176 Ye L, Lin R, Fan Y, Yang L, Hu J and Shu Q (2013). Effects of circuit residual volume salvage reinfusion on the postoperative clinical outcome for pediatric patients undergoing cardiac surgery, *Pediatric Cardiology* 34(5):1088–1093. <http://link.springer.com/article/10.1007%2Fs00246-012-0606-z>

177 Nakayama Y, Nakajima Y, Tanaka KA, Sessler DI, Maeda S, Iida J, et al. (2015). Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery, *Br J Anaesth* 114(1):91–102. <http://www.ncbi.nlm.nih.gov/pubmed/25303988>

178 Arnold DM, Fergusson DA, Chan AKC, Cook RJ, Fraser GA, Lim W, et al. (2006). Avoiding transfusions in children undergoing cardiac surgery: A meta-analysis of randomized trials of aprotinin, *Anesthesia and Analgesia* 102(3):731–737. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L43306387>

179 Faraoni D and Goobie SM (2014). The efficacy of antifibrinolytic drugs in children undergoing noncardiac surgery: A systematic review of the literature, *Anesthesia and Analgesia* 118(3):628–636. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372489518>

<http://dx.doi.org/10.1213/ANE.0000000000000080>

180 Ker K, Beecher D and Roberts I (2013). Topical application of tranexamic acid for the reduction of bleeding, *Cochrane Database of Systematic Reviews*.

181 Schouten ES, Van De Pol AC, Schouten ANJ, Turner NM, Jansen NJG and Bollen CW (2009). The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: A meta-analysis, *Pediatric Critical Care Medicine* 10(2):182–190. <http://dx.doi.org/10.1097/PCC.0b013e3181956d61>

182 Song G, Yang P, Zhu S, Luo E, Feng G, Hu J, et al. (2013). Tranexamic acid reducing blood transfusion in children undergoing craniosynostosis surgery, *Journal of Craniofacial Surgery* 24(1):299–303. <http://dx.doi.org/10.1097/SCS.0b013e3182710232>

183 Tzortzopoulou A, Cepeda MS, Schumann R and Carr DB (2008). Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children, *Cochrane Database of Systematic Reviews*.

184 Basta MN, Stricker PA and Taylor JA (2012). A systematic review of the use of antifibrinolytic agents in pediatric surgery and implications for craniofacial use, *Pediatr Surg Int* 28(11):1059-1069. <http://www.ncbi.nlm.nih.gov/pubmed/22940882>

185 Badeaux J and Hawley D (2014). A systematic review of the effectiveness of intravenous tranexamic acid administration in managing perioperative blood loss in patients undergoing spine surgery, *J Perianesth Nurs* 29(6):459-465. <http://www.ncbi.nlm.nih.gov/pubmed/25458625>

186 Aggarwal V, Kapoor PM, Choudhury M, Kiran U and Chowdhury U (2012). *Utility of sonoclot analysis and tranexamic acid in tetralogy of Fallot patients undergoing intracardiac repair*, 15:26–31.

187 Coniff RF, Ceithaml EL, Pourmojhadam K, D'Errico CC, Dietrich W and Greeley WJ (1998). Bayer 022 compassionate-use pediatric study, *Annals of Thoracic Surgery* 65(6 SUPPL.):S31–S34. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L28308473>

188 Ferreira CA, de Andrade Vicente WV, Evora PRB, Rodrigues AJ, Klamt JG, de Carvalho Panzeli Carlotti AP, et al. (2010). Assessment of aprotinin in the reduction of inflammatory systemic response in children undergoing surgery with cardiopulmonary bypass, *Brazilian Journal of Cardiovascular Surgery* 25(1):85–98. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L359111284>

189 Flaujac C, Pouard P, Boutouyrie P, Emmerich J, Bachelot-Loza C and Lasne D (2007). Platelet dysfunction after normothermic cardiopulmonary bypass in children: Effect of high-dose aprotinin, *Thrombosis and Haemostasis* 98(2):385–391. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L47250242>

190 Sarupria A, Makhija N, Lakshmy R and Kiran U (2013). Comparison of different doses of (epsilon)-aminocaproic acid in children for tetralogy of fallot surgery: Clinical efficacy and safety, *Journal of Cardiothoracic and Vascular Anesthesia* 27(1):23–29. <http://www.jcvaonline.com/article/S1053-0770(12)00344-8/abstract>

191 Singh R, Manimozhi V, Nagaraj G, Vasanth K, Sanjay KB, John C, et al. (2001). Aprotinin for open cardiac surgery in cyanotic heart disease, *Asian Cardiovascular and Thoracic Annals* 9(2):101–104. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L32618900>

192 Vacharaksa K, Prakanrattana U, Suksompong S and Chumpathong S (2002). Tranexamic acid as a means of reducing the need for blood and blood component therapy in children undergoing open heart surgery for congenital cyanotic heart disease, *Journal of the Medical Association of Thailand* 85(SUPPL. 3):S904–S909. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36025031>

193 Thompson GH, Florentino-Pineda I and Poe-Kochert C (2005). *The Role of Amicar in Decreasing Perioperative Blood Loss in Idiopathic Scoliosis* 30:S94–S99.

194 Verma K, Errico T, Diefenbach C, Hoelscher C, Peters A, Dryer J, et al. (2014). The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: A prospective randomized trial, *Journal of Bone and Joint Surgery American Volume* 96:e80–e80.

195 Ahmed Z, Stricker L, Rozzelle A and Zestos M (2014). *Aprotinin and transfusion requirements in pediatric craniofacial surgery*, 24:141–145.

196 D'Errico CC, Munro HM, Buchman SR, Wagner D and Muraszko KM (2003). *Efficacy of aprotinin in children undergoing craniofacial surgery*, 99:287–290.

197 Eldaba AA, Amr YM and Albirmawy OA (2013). Effects of tranexamic acid during endoscopic sinsus surgery in children, *Saudi Journal of Anaesthesia* 7:229–233. <http://www.saudija.org/article.asp?issn=1658-354X;year=2013;volume=7;issue=3;spage=229;epage=233;aulast=Eldaba>

198 Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL and Blakemore LC (2004). *The effect of Amicar in perioperative blood loss in idiopathic scoliosis. The results of a prospective, randomized double-blind study*, 29:233–238.

199 Khoshhal K, Mukhtar I, Clark P, Jarvis J, Letts M and Splinter W (2003). *Efficacy of aprotinin in reducing blood loss in spinal fusion for idiopathic scoliosis*, 23:661–664.

200 Neilipovitz D, Murto K, Hall L, Barrowman N and Splinter W (2001). *A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery*, 93:82–87.

201 Sethna NF, Zurakowski D, Brustowicz M, Bacsik J, Sullivan L and Shapiro F (2005). *Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery*, 102:727–732.

202 Dadure C, Sauter M, Bringuier S, Bigorre M, Raux O, Rochette A, et al. (2011). Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniosynostosis surgery: a randomized double-blind study, *Anesthesiology* 114:856–861. <http://anesthesiology.pubs.asahq.org/data/Journals/JASA/931106/0000542-201104000-00020.pdf>

203 Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, et al. (2011). Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial, *Anesthesiology* 114:862–871. <http://anesthesiology.pubs.asahq.org/data/Journals/JASA/931106/0000542-201104000-00021.pdf>

204 Maugans TA, Martin D, Taylor J, Salisbury S and Istaphanous G (2011). Comparative analysis of tranexamic acid use in minimally invasive versus open craniosynostosis procedures, *J Craniofac Surg* 22(5):1772-1778. <http://www.ncbi.nlm.nih.gov/pubmed/21959429>

205 Albirmawy OA, Saafan ME, Shehata EM, Basuni AS and Eldaba AA (2013). Topical application of tranexamic acid after adenoidectomy: A double-blind, prospective, randomized, controlled study, *International Journal of Pediatric Otorhinolaryngology* 77:1139–1142. <http://www.ijporlonline.com/article/S0165-5876(13)00180-8/abstract>

206 Cole JW, Murray DJ, Snider RJ, Bassett GS, Bridwell KH and Lenke LG (2003). *Aprotinin reduces blood loss during spinal surgery in children*, 28:2482–2485.

207 Faraoni D, Willems A, Melot C, De Hert S and Van der Linden P (2012). Efficacy of tranexamic acid in paediatric cardiac surgery: A systematic review and meta-analysis, *European Journal of Cardio-Thoracic Surgery* 42(5):781–786. <http://ejcts.oxfordjournals.org/content/42/5/781.full.pdf>

208 Chauhan S, Das SN, Bisoi A, Kale S and Kiran U (2004a). Comparison of Epsilon Aminocaproic Acid and Tranexamic Acid in Pediatric Cardiac Surgery, *Journal of Cardiothoracic and Vascular Anesthesia* 18(2):141–143. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L38506857>

<http://www.jcvaonline.com/article/S1053-0770(04)00029-1/abstract>

209 Brum MR, Miura MS, Castro SF, Machado GM, Lima LH and Lubianca-Neto JF (2012). Tranexamic acid in adenotonsillectomy in children: a double-blind randomized clinical trial, *International Journal of Pediatric Otorhinolaryngology* 76:1401–1405. <http://www.ijporlonline.com/article/S0165-5876(12)00292-3/abstract>

210 Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M, et al. (2012). Comparative analysis of antifibrinolytic medications in pediatric heart surgery, *J Thorac Cardiovasc Surg* 143(3):550-557. <http://www.ncbi.nlm.nih.gov/pubmed/22264414>

211 Goobie SM, Meier PM, Sethna NF, Soriano SG, Zurakowski D, Samant S, et al. (2013). Population pharmacokinetics of tranexamic acid in paediatric patients undergoing craniosynostosis surgery, *Clin Pharmacokinet* 52(4):267-276. <http://www.ncbi.nlm.nih.gov/pubmed/23371895>

212 Wesley MC, Pereira LM, Scharp LA, Emani SM, McGowan FX, Jr. and DiNardo JA (2015). Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass, *Anesthesiology* 122(4):746–758. <http://www.ncbi.nlm.nih.gov/pubmed/25585004>

213 Simpson E, Lin Y, Stanworth S, Birchall J, Doree C and Hyde C (2012). Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia, *Cochrane Database of Systematic Reviews*.

214 Ekert H, Brizard C, Eyers R, Cochrane A and Henning R (2006). Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions, *Blood Coagulation and Fibrinolysis* 17(5):389–395. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L43941581>

215 Mozol K, Haponiuk I, Byszewski A and Maruszewski B (2008). Cost-effectiveness of mini-circuit cardiopulmonary bypass in newborns and infants undergoing open heart surgery, *Kardiologia.Polska* 66:925–931.

216 CATSIN (2013). *Towards a shared understanding of terms and concepts: strengthening nursing and midwifery care of Aboriginal and Torres Strait Islander peoples*, Congress of Aboriginal and Torres Strait Islander Nurses (CATSIN), Canberra.

217 Holland C (2015). *Close the gap: progress and priorities report 2015*, Australian Human Rights Commission, Sydney.

218 Coffin J (2007). Rising to the challenge in Aboriginal health by creating cultural security, *Aboriginal and Islander Health Worker Journal* 31(3):22–24.

219 Department of Health GoWA (2003). *Aboriginal cultural security: a background paper*, Government of Western Australia, Perth.

220 Dudgeon P, Wright M and Coffin J (2010). Talking It and Walking It: Cultural Competence, 13(3):29–44.

221 Dunbar T (2011). Aboriginal people's experiences of health and family services in the Northern Territory, 4(2):2–16.

222 Kruske S, Kildea S and Barclay L (2006). Cultural safety and maternity care for Aboriginal and Torres Strait Islander Australians, *Women and Birth ; Journal of the Australian College of Midwives* 19(3):73–77.

223 Reibel T and Walker R (2010). Antenatal services for Aboriginal women: the relevance of cultural competence, *Quality in Primary Care* 18(1):65–74.

224 Taylor K and Guerin P (2010). *Health care and Indigenous Australians: Cultural safety in practice*, Palgrave McMillan, South Yarra.

225 Kildea S and Wagner VV (2013). *'Birthing on Country' maternity service delivery models: a rapid review An Evidence Check review brokered by the Sax Institute for the Maternity Services Inter-Jurisdictional Committee Maternity Services Inter Jurisdictional Committee for the Australian Health Ministers’ Advisory Council*, Sax Institute and Maternity Services Inter-Jurisdictional Committee Maternity Services Inter Jurisdictional Committee, Sydney. <http://www.researchgate.net/publication/265554018_'Birthing_on_Country'_maternity_service_delivery_models_a_rapid_review_An_Evidence_Check_review_brokered_by_the_Sax_Institute_for_the_Maternity_Services_Inter-Jurisdictional_Committee_Maternity_Services_Inter_Jurisdictional_Committee>

226 Australian Institute of Health and Welfare (AIHW) (2011). *The health and welfare of Australia’s Aboriginal and Torres Strait Islander people*, Cat. No. IHW 42, AIHW, Canberra.

227 Holt DC, McCarthy JS and Carapetis JR (2010). Parasitic diseases of remote Indigenous communities in Australia, *Int J Parasitol* 40(10):1119-1126. <http://www.ncbi.nlm.nih.gov/pubmed/20412810>

228 Windsor HM, Abioye-Kuteyi EA, Leber JM, Morrow SD, Bulsara MK and Marshall BJ (2005). Prevalence of Helicobacter pylori in Indigenous Western Australians: comparison between urban and remote rural populations, *Med J Aust* 182(5):210-213. <http://www.ncbi.nlm.nih.gov/pubmed/15748129>

229 Li Z, Zeki R, L H and Sullivan EA (2011). *Australia's mothers and babies*, Perinatal statistics series, No. 28, Australian Institute of Health and Welfare.

230 Australian Institute of Health and Welfare (AIHW) (2015). *The health and welfare of Australia’s Aboriginal and Torres Strait Islander people*, Cat. No. IHW 147, AIHW, Canberra.

231 Kumar A, Jain S, Singh NP and Singh T (2005). Oral versus high dose parenteral iron supplementation in pregnancy, *International Journal of Gynaecology and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics* 89(1):7–13.

232 Hess JR and Greenwalt TG (2002). Storage of red blood cells: new approaches, *Transfus Med Rev* 16(4):283–295. <http://www.ncbi.nlm.nih.gov/pubmed/12415514>

233 Triulzi DJ and Yazer MH (2010). Clinical studies of the effect of blood storage on patient outcomes, *Transfus Apher Sci* 43(1):95–106. <http://www.ncbi.nlm.nih.gov/pubmed/20656558>

234 Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P, et al. (2004). Transfusion guidelines for neonates and older children, *Br J Haematol* 124(4):433–453. <http://www.ncbi.nlm.nih.gov/pubmed/14984493>

235 Kennedy MS (2011). Perinatal issues in transfusion practice, In Roback JD, Grossman BJ, et al. (eds.), *Technical Manual*, AABB, Bethesda, MD, 631–644.

236 Strauss RG (2010). RBC storage and avoiding hyperkalemia from transfusions to neonates & infants, *Transfusion* 50(9):1862–1865. <http://www.ncbi.nlm.nih.gov/pubmed/21552366>

237 *Exchange transfusion: Neonatal*, Royal Children's Hospital, Melbourne. <http://www.rch.org.au/uploadedFiles/Main/Content/neonatal_rch/EXCHANGE_TRANSFUSION.pdf>

238 Ramasethu J (2012). Exchange transfusion, In MacDonald M, Ramasethu J, et al. (eds.), *Atlas of procedures in neonatology, Fifth edition* Wolters Kluwer/Lippincott Williams & Wilkins.

239 UK Blood Transfusion & Tissue Transplantation Services (2013). *Guidelines for the blood tranfusion services in the United Kingdom*, The Stationary Office, London.

240 ANZSBT (2007). *Guidelines for pretransfusion laboratory practice*, 3rd Edition, Australian & New Zealand Society of Blood Transfusion Inc (ANZSBT). [www.anzsbt.org.au/publications/documents/PLP\_Guidelines\_Mar07.pdf](http://www.anzsbt.org.au/publications/documents/PLP_Guidelines_Mar07.pdf)

241 Ranucci M, Carlucci C, Isgro G, Boncilli A, De Benedetti D, De la Torre T, et al. (2009). Duration of red blood cell storage and outcomes in pediatric cardiac surgery: an association found for pump prime blood, *Crit Care* 13(6):R207. <http://www.ncbi.nlm.nih.gov/pubmed/20025760>

242 Fergusson DA, Hebert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, et al. (2012). Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial, *JAMA* 308(14):1443–1451. <http://www.ncbi.nlm.nih.gov/pubmed/23045213>

243 Gauvin F, Spinella PC, Lacroix J, Choker G, Ducruet T, Karam O, et al. (2010). Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients, *Transfusion* 50(9):1902–1913. <http://www.ncbi.nlm.nih.gov/pubmed/20456697>

244 Karam O, Tucci M, Bateman ST, Ducruet T, Spinella PC, Randolph AG, et al. (2010). Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study, *Crit Care* 14(2):R57. <http://www.ncbi.nlm.nih.gov/pubmed/20377853>

245 ANZSBT (2007). *Guidelines for blood grouping & antibody screening in the antenatal & perinatal setting*, 3rd Edition, Australian & New Zealand Society of Blood Transfusion Inc (ANZSBT). <http://www.anzsbt.org.au/publications/documents/Antenatal_Guidelines_Mar07.pdf>

246 van Wamelen DJ, Klumper FJ, de Haas M, Meerman RH, van Kamp IL and Oepkes D (2007). Obstetric history and antibody titer in estimating severity of Kell alloimmunization in pregnancy, *Obstet Gynecol* 109(5):1093–1098. <http://www.ncbi.nlm.nih.gov/pubmed/17470588>

247 (2013). *Handbook of transfusion medicine (5th edition)*, United Kingdom Blood Services, TSO. <http://www.transfusionguidelines.org.uk/transfusion-handbook>

248 Vamvakas EC (2005). Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis, *Transfus Med Rev* 19(3):181–199. <http://www.tmreviews.com/article/S0887-7963(05)00012-X/abstract>

249 Preiksaitis JK (2000). The cytomegalovirus-"safe" blood product: is leukoreduction equivalent to antibody screening?, *Transfus Med Rev* 14(2):112–136. <http://www.tmreviews.com/article/S0887-7963(00)80003-6/abstract>

250 Drew WL and Roback JD (2007). Prevention of transfusion-transmitted cytomegalovirus: reactivation of the debate?, *Transfusion* 47(11):1955–1958. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2007.01494.x/abstract>

251 Seed CR, Wong J, Polizzotto MN, Faddy H, Keller AJ and Pink J (2015). The residual risk of transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components, *Vox Sang* 109(1):11-17. <http://www.ncbi.nlm.nih.gov/pubmed/25854287>

252 Roback JD, Conlan M, Drew WL, Ljungman P, Nichols WG and Preiksaitis JK (2006). The role of photochemical treatment with amotosalen and UV-A light in the prevention of transfusion-transmitted cytomegalovirus infections, *Transfus Med Rev* 20(1):45–56. <http://www.tmreviews.com/article/S0887-7963(05)00081-7/abstract>

253 Canadian Blood Services (2011). CMV seronegative, irradiated and washed blood components, *Clinical guide to transfusion*. <http://www.transfusionmedicine.ca/resources/clinical-guide-transfusion>

254 American Association of Blood Banks (1997). *Statement of the American Association of Blood Banks Before the Blood Products Advisory Committee on the Effect of Leukoreduction on CMV Transmission Through Blood Transfusion. AABB Bulletin #97-2*. <http://www.aabb.org/advocacy/statements/Pages/cmvstate.aspx>

255 Advisory Committee on the Safety of Blood (2012). *Cytomegalovirus tested blood components: Position Statement. SaBTO report of the Cytomegalovirus Steering Group*, Department of Health. <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215125/dh_133086.pdf>

256 Thiele T, Kruger W, Zimmermann K, Ittermann T, Wessel A, Steinmetz I, et al. (2011). Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME), *Transfusion* 51(12):2620–2626. <http://www.ncbi.nlm.nih.gov/pubmed/21645009>

257 Nash T, Hoffmann S, Butch S, Davenport R and Cooling L (2012). Safety of leukoreduced, cytomegalovirus (CMV)-untested components in CMV-negative allogeneic human progenitor cell transplant recipients, *Transfusion* 52(10):2270–2272. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2012.03739.x/abstract>

258 Curtis BR and McFarland JG (2014). Human platelet antigens - 2013, *Vox Sang* 106(2):93–102. <http://www.ncbi.nlm.nih.gov/pubmed/24102564>

259 Mueller-Eckhardt C KV, Grubert A et al. (1989). 348 cases of suspected neonatal alloimmune thrombocytopenia, *The Lancet* 1:363–366.

260 Davoren A CBR, Aster R.H, McFarland J.G (2004). Human platelet antigen-specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia, *Transfusion* 44:1220–1225.

261 Bennett JA, Palmer LJ, Musk AW and Erber WN (2002). Gene frequencies of human platelet antigens 1-5 in indigenous Australians in Western Australia, *Transfus Med* 12(3):199–203. <http://www.ncbi.nlm.nih.gov/pubmed/12071877>

262 Sainio S, Jarvenpaa AL, Renlund M, Riikonen S, Teramo K and Kekomaki R (2000). Thrombocytopenia in term infants: a population-based study, *Obstet Gynecol* 95(3):441-446. <http://www.ncbi.nlm.nih.gov/pubmed/10711560>

263 Spencer JA and Burrows RF (2001). Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis, *Aust N Z J Obstet Gynaecol* 41(1):45–55. <http://www.ncbi.nlm.nih.gov/pubmed/11284646>

264 Risson D.C DMWaWBA (2012). Review of neonatal alloimmune thrombocytopenia, *Journal of Paediatrics and Child Health* 48:816–822.

265 Bakchoul T BD, Heckmann M et al. (2014). Management of infants born with severe neonatal alloimmune thrombocytopenia: the role of platelet transfusions and intravenous immunoglobulin, *Transfusion* 54(3):640–645.

266 Kiefel V BD, Kroll H et al (2006). Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT), *Blood* 107:3761–3763.

267 Win N, Ouwehand WH and Hurd C (1997). Provision of platelets for severe neonatal thrombocytopenia, *Br J Haematol* 97:927–940.

268 Stroncek DF and Rebulla P (2007). Platelet transfusions, *Lancet* 370(9585):427–438. <http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61198-2/abstract>

269 Williamson LM (2000). Leucocyte depletion of the blood supply - how will patients benefit?, *Br J Haematol* 110(2):256–272. <http://onlinelibrary.wiley.com/store/10.1046/j.1365-2141.2000.02062.x/asset/j.1365-2141.2000.02062.x.pdf?v=1&t=i8wruya2&s=74f48e82a7df96b9a8b15ab677ecae24b0c0c831>

270 Nahirniak S, Slichter SJ, Tanael S, Rebulla P, Pavenski K, Vassallo R, et al. (2015). Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia, *Transfus Med Rev* 29(1):3–13. <http://www.ncbi.nlm.nih.gov/pubmed/25537844>

271 Bolton-Maggs PH, Chalmers EA, Collins PW, Harrison P, Kitchen S, Liesner RJ, et al. (2006). A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO, *Br J Haematol* 135(5):603–633. <http://onlinelibrary.wiley.com/store/10.1111/j.1365-2141.2006.06343.x/asset/j.1365-2141.2006.06343.x.pdf?v=1&t=i8wrvnos&s=294e42b570fc55c125e469ffef68e4f32b8215a3>

272 Schlegel N, Bardet V, Kenet G, Muntean W, Zieger B, Nowak-Gottl U, et al. (2010). Diagnostic and therapeutic considerations on inherited platelet disorders in neonates and children, *Klinische Padiatrie* 222(3):209–214. <https://www.thieme-connect.com/DOI/DOI?10.1055/s-0030-1249065>

273 Blumberg N, Heal JM and Rowe JM (2004). A randomized trial of washed red blood cell and platelet transfusions in adult acute leukemia [ISRCTN76536440], *BMC blood disorders* 4(1):6. <http://www.ncbi.nlm.nih.gov/pubmed/15588315>

274 Blumberg N, Heal JM, Gettings KF, Phipps RP, Masel D, Refaai MA, et al. (2010). An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions, *Transfusion* 50(12):2738–2744. <http://www.ncbi.nlm.nih.gov/pubmed/20561296>

275 Belizaire RM, Makley AT, Campion EM, Sonnier DI, Goodman MD, Dorlac WC, et al. (2012). Resuscitation with washed aged packed red blood cell units decreases the proinflammatory response in mice after hemorrhage, *J Trauma Acute Care Surg* 73(2 Suppl 1):S128–133. <http://www.ncbi.nlm.nih.gov/pubmed/22847082>

276 Moise K (2013). Intrauterine fetal transfusion of red blood cells, In Lockwood C & Barss V (eds.), *UpToDate*. <http://www.uptodate.com/contents/intrauterine-fetal-transfusion-of-red-blood-cells>

277 Cholette JM, Henrichs KF, Alfieris GM, Powers KS, Phipps R, Spinelli SL, et al. (2012). Washing red blood cells and platelets transfused in cardiac surgery reduces postoperative inflammation and number of transfusions: results of a prospective, randomized, controlled clinical trial, *Pediatr Crit Care Med* 13(3):290–299. <http://www.ncbi.nlm.nih.gov/pubmed/21926663>

278 Hosking MP, Beynen FM, Raimundo HS, Oliver WC, Jr. and Williamson KR (1990). A comparison of washed red blood cells versus packed red blood cells (AS-1) for cardiopulmonary bypass prime and their effects on blood glucose concentration in children, *Anesthesiology* 72(6):987–990. <http://www.ncbi.nlm.nih.gov/pubmed/2112346>

279 Swindell CG, Barker TA, McGuirk SP, Jones TJ, Barron DJ, Brawn WJ, et al. (2007). Washing of irradiated red blood cells prevents hyperkalaemia during cardiopulmonary bypass in neonates and infants undergoing surgery for complex congenital heart disease, *Eur J Cardiothorac Surg* 31(4):659–664. <http://www.ncbi.nlm.nih.gov/pubmed/17291775>

280 Strauss RG (2000). Data-driven blood banking practices for neonatal RBC transfusions, *Transfusion* 40(12):1528–1540. <http://www.ncbi.nlm.nih.gov/pubmed/11134575>

281 van Kamp IL, Klumper FJCM, Meerman RH, Oepkes D, Scherjon SA and Kanhai HH (2004). Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in the Netherlands, 1988-1999, *Acta Obstetricia et Gynecologica Scandinavica* 83(8):731–737. <http://onlinelibrary.wiley.com/doi/10.1111/j.0001-6349.2004.00394.x/abstract>

282 Somerset DA, Moore A, Whittle MJ, Martin W and Kilby MD (2006). An audit of outcome in intravascular transfusions using the intrahepatic portion of the fetal umbilical vein compared to cordocentesis, *Fetal Diagnosis and Therapy* 21(3):272–276.

283 Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ, Jr., et al. (2000). Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses, *N Engl J Med* 342(1):9–14. <http://www.ncbi.nlm.nih.gov/pubmed/10620643>

284 Scheier M, Hernandez-Andrade E, Fonseca EB and Nicolaides KH (2006). Prediction of severe fetal anemia in red blood cell alloimmunization after previous intrauterine transfusions, *Am J Obstet Gynecol* 195(6):1550–1556. <http://www.ajog.org/article/S0002-9378(06)00447-9/abstract>

285 Detti L, Oz U, Guney I, Ferguson JE, Bahado-Singh RO, Mari G, et al. (2001). Doppler ultrasound velocimetry for timing the second intrauterine transfusion in fetuses with anemia from red cell alloimmunization, *Am J Obstet Gynecol* 185(5):1048–1051. <http://www.ncbi.nlm.nih.gov/pubmed/11717631>

286 Wong KS, Connan K, Rowlands S, Kornman LH and Savoia HF (2013). Antenatal immunoglobulin for fetal red blood cell alloimmunization, *Cochrane Database Syst Rev* 5:CD008267. <http://www.ncbi.nlm.nih.gov/pubmed/23728672>

287 Van Kamp IL, Klumper FJCM, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FP, et al. (2005). Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization, *Am J Obstet Gynecol* 192(1):171–177.

288 Canlorbe G, Mace G, Cortey A, Cynober E, Castaigne V, Larsen M, et al. (2011). Management of very early fetal anemia resulting from red-cell alloimmunization before 20 weeks of gestation, *Obstetrics and Gynecology* 118(6):1323–1329.

289 Bateman ST, Lacroix J, Boven K, Forbes P, Barton R, Thomas NJ, et al. (2008). Anemia, blood loss, and blood transfusions in North American children in the intensive care unit, *Am J Respir Crit Care Med* 178(1):26–33. <http://www.ncbi.nlm.nih.gov/pubmed/18420962>

290 Bednarek FJ, Weisberger S, Richardson DK, Frantz ID, 3rd, Shah B and Rubin LP (1998). Variations in blood transfusions among newborn intensive care units. SNAP II Study Group, *J Pediatr* 133(5):601–607. <http://www.ncbi.nlm.nih.gov/pubmed/9821414>

291 Valentine SL and Bateman ST (2012). Identifying factors to minimize phlebotomy-induced blood loss in the pediatric intensive care unit, *Pediatr Crit Care Med* 13(1):22–27. <http://www.ncbi.nlm.nih.gov/pubmed/21499175>

292 Lin JC, Strauss RG, Kulhavy JC, Johnson KJ, Zimmerman MB, Cress GA, et al. (2000). Phlebotomy overdraw in the neonatal intensive care nursery, *Pediatrics* 106(2):E19. <http://www.ncbi.nlm.nih.gov/pubmed/10920175>

293 Raju TN, Stevenson DK, Higgins RD and Stark AR (2009). Safe and effective devices and instruments for use in the neonatal intensive care units: NICHD Workshop summary, *Biomed Instrum Technol* 43(5):408–418. <http://www.ncbi.nlm.nih.gov/pubmed/19842778>

294 Obladen M, Sachsenweger M and Stahnke M (1988). Blood sampling in very low birth weight infants receiving different levels of intensive care, *Eur J Pediatr* 147(4):399–404. <http://www.ncbi.nlm.nih.gov/pubmed/3396595>

295 Barie PS and Hydo LJ (1997). Lessons learned: durability and progress of a program for ancillary cost reduction in surgical critical care, *J Trauma* 43(4):590-594; discussion 594-596. <http://www.ncbi.nlm.nih.gov/pubmed/9356053>

296 Roberts DE, Bell DD, Ostryzniuk T, Dobson K, Oppenheimer L, Martens D, et al. (1993). Eliminating needless testing in intensive care--an information-based team management approach, *Crit Care Med* 21(10):1452-1458. <http://www.ncbi.nlm.nih.gov/pubmed/8403952>

297 Prat G, Lefevre M, Nowak E, Tonnelier JM, Renault A, L'Her E, et al. (2009). Impact of clinical guidelines to improve appropriateness of laboratory tests and chest radiographs, *Intensive Care Med* 35(6):1047-1053. <http://www.ncbi.nlm.nih.gov/pubmed/19221715>

298 Carroll PD and Widness JA (2012). Nonpharmacological, blood conservation techniques for preventing neonatal anemia--effective and promising strategies for reducing transfusion, *Semin Perinatol* 36(4):232-243. <http://www.ncbi.nlm.nih.gov/pubmed/22818543>

299 McEvoy MT and Shander A (2013). Anemia, bleeding, and blood transfusion in the intensive care unit: causes, risks, costs, and new strategies, *Am J Crit Care* 22(6 Suppl):eS1-13; quiz eS14. <http://www.ncbi.nlm.nih.gov/pubmed/24186829>

300 Christensen RD, Carroll PD and Josephson CD (2014). Evidence-based advances in transfusion practice in neonatal intensive care units, *Neonatology* 106(3):245-253. <http://www.ncbi.nlm.nih.gov/pubmed/25300949>

301 Bishara N and Ohls RK (2009). Current controversies in the management of the anemia of prematurity, *Semin Perinatol* 33(1):29-34. <http://www.ncbi.nlm.nih.gov/pubmed/19167579>

302 Shander A and Goodnough LT (2006). Objectives and limitations of bloodless medical care, *Curr Opin Hematol* 13(6):462-470. <http://www.ncbi.nlm.nih.gov/pubmed/17053460>

303 Weiss M, Fischer J, Boeckmann M, Rohrer B and Baenziger O (2001). Evaluation of a simple method for minimizing iatrogenic blood loss from discard volumes in critically ill newborns and children, *Intensive Care Med* 27(6):1064–1072. <http://www.ncbi.nlm.nih.gov/pubmed/11497140>

304 Page C, Retter A and Wyncoll D (2013). Blood conservation devices in critical care: a narrative review, *Ann Intensive Care* 3:14. <http://www.ncbi.nlm.nih.gov/pubmed/23714376>

305 Tang M, Feng M, Chen L, Zhang J, Ji P and Luo S (2014). Closed blood conservation device for reducing catheter-related infections in children after cardiac surgery, *Crit Care Nurse* 34(5):53–60; quiz 61. <http://www.ncbi.nlm.nih.gov/pubmed/25274764>

306 Billman GF, Hughes AB, Dudell GG, Waldman E, Adcock LM, Hall DM, et al. (2002). Clinical performance of an in-line, ex vivo point-of-care monitor: a multicenter study, *Clin Chem* 48(11):2030–2043. <http://www.ncbi.nlm.nih.gov/pubmed/12406990>

307 Widness JA, Madan A, Grindeanu LA, Zimmerman MB, Wong DK and Stevenson DK (2005). Reduction in red blood cell transfusions among preterm infants: results of a randomized trial with an in-line blood gas and chemistry monitor, *Pediatrics* 115(5):1299–1306. <http://www.ncbi.nlm.nih.gov/pubmed/15867038>

308 Australian Red Cross Blood Service (2012). *Blood component information: circular of information*. <http://resources.transfusion.com.au/cdm/ref/collection/p16691coll1/id/135>

309 CSL Limited (Bioplasma Division) *Prothrombinex-VF product information*. <http://www.csl.com.au/productfinder/prothrombinexau>

310 Sarode R, Milling TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. (2013). Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study, *Circulation* 128(11):1234–1243. <http://circ.ahajournals.org/content/128/11/1234.full.pdf>

311 Voils SA and Baird B (2012). Systematic review: 3-factor versus 4-factor prothrombin complex concentrate for warfarin reversal: does it matter?, *Thrombosis Research* 130(6):833–840. <http://www.thrombosisresearch.com/article/S0049-3848(12)00759-1/abstract>

312 Demeyere R, Gillardin S, Arnout J and Strengers PF (2010). Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study, *Vox Sanguinis* 99(3):251–260. <http://onlinelibrary.wiley.com/doi/10.1111/j.1423-0410.2010.01339.x/abstract>

313 Giorni C, Ricci Z, Iodice F, Garisto C, Favia I, Polito A, et al. (2014). Use of Confidex to control perioperative bleeding in pediatric heart surgery: prospective cohort study, *Pediatr Cardiol* 35(2):208-214. <http://www.ncbi.nlm.nih.gov/pubmed/23843105>

314 Arnekian V, Camous J, Fattal S, Rezaiguia-Delclaux S, Nottin R and Stephan F (2012). Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery, *Interactive Cardiovascular and Thoracic Surgery* 15(3):382–389. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422937/pdf/ivs224.pdf>

315 Bobbitt L, Merriman E, Raynes J, Henderson R, Blacklock H and Chunilal S (2011). PROTHROMBINEX((R))-VF (PTX-VF) usage for reversal of coagulopathy: prospective evaluation of thrombogenic risk, *Thrombosis Research* 128(6):577–582. <http://www.thrombosisresearch.com/article/S0049-3848(11)00180-0/abstract>

316 Streiff MB (2011). Prothrombin complex concentrates for reversal of vitamin K antagonists: assessing the risks, *Thrombosis and Haemostasis* 106(3):389–390.

317 Dentali F, Marchesi C, Pierfranceschi MG, Crowther M, Garcia D, Hylek E, et al. (2011). Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis, *Thrombosis and Haemostasis* 106(3):429–438.

318 Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, et al. (2012). Transfusion-related acute lung injury: incidence and risk factors, *Blood* 119(7):1757–1767. <http://www.bloodjournal.org/content/bloodjournal/119/7/1757.full.pdf>

319 Alam A, Lin Y, Lima A, Hansen M and Callum JL (2013). The prevention of transfusion-associated circulatory overload, *Transfus Med Rev* 27(2):105–112. <http://www.tmreviews.com/article/S0887-7963(13)00005-9/abstract>

320 Popovsky MA (2006). Pulmonary consequences of transfusion: TRALI and TACO, *Transfusion and Apheresis Science* 34(3):243–244. <http://www.trasci.com/article/S1473-0502(06)00054-1/abstract>

321 Serious Hazards of T (2011). Annual SHOT Report. <http://www.shotuk.org/wp-content/uploads/2012/07/SHOT-Summary_FinalWebVersion2012_06_261.pdf>

322 Li G, Rachmale S, Kojicic M, Shahjehan K, Malinchoc M, Kor DJ, et al. (2011). Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients, *Transfusion* 51(2):338–343. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3006039/pdf/nihms219753.pdf>

323 Narick C, Triulzi DJ and Yazer MH (2012). Transfusion-associated circulatory overload after plasma transfusion, *Transfusion* 52(1):160–165. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2011.03247.x/abstract>

324 Zou S, Dorsey KA, Notari EP, Foster GA, Krysztof DE, Musavi F, et al. (2010). Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing, *Transfusion* 50(7):1495–1504. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2010.02622.x/abstract>

325 Zou S, Stramer SL, Notari EP, Kuhns MC, Krysztof D, Musavi F, et al. (2009). Current incidence and residual risk of hepatitis B infection among blood donors in the United States, *Transfusion* 49(8):1609–1620. <http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2009.02195.x/abstract>

326 Pace Napoleone C, Valori A, Crupi G, Ocello S, Santoro F, Vouhe P, et al. (2009). An observational study of CoSeal for the prevention of adhesions in pediatric cardiac surgery, 9(6):978–982. <http://icvts.oxfordjournals.org/content/9/6/978.full.pdf>

327 Kuschel TJ, Gruszka A, Hermanns-Sachweh B, Elyakoubi J, Sachweh JS, Vazquez-Jimenez JF, et al. (2013). Prevention of postoperative pericardial adhesions with TachoSil, *The Annals of Thoracic Surgery* 95(1):183–188. <http://www.annalsthoracicsurgery.org/article/S0003-4975(12)01889-9/pdf>

328 Tackett SM, Sugarman R, Kreuwel HTC, Alvarez P and Nasso G (2014). Hospital economic impact from hemostatic matrix usage in cardiac surgery, *Journal of Medical Economics* 17(9):670–676. <http://informahealthcare.com/doi/pdfplus/10.3111/13696998.2014.928638>

329 LeMaire SA, Schmittling ZC, Coselli JS, Undar A, Deady BA, Clubb FJ, et al. (2002). BioGlue surgical adhesive impairs aortic growth and causes anastomotic strictures, *The Annals of Thoracic Surgery* 73(5):1500–1505, discussion 1506. <http://www.annalsthoracicsurgery.org/article/S0003-4975(02)03512-9/pdf>

330 Ortel TL, Mercer MC, Thames EH, Moore KD and Lawson JH (2001). Immunologic impact and clinical outcomes after surgical exposure to bovine thrombin, *Annals of Surgery* 233(1):88–96. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1421171/pdf/20010100s00014p88.pdf>

331 Cauchy F, Gaujoux S, Ronot M, Fuks D, Dokmak S, Sauvanet A, et al. (2014). Local venous thrombotic risk of an expanding haemostatic agent used during liver resection, *World Journal of Surgery* 38(9):2363–2369. <http://link.springer.com/article/10.1007%2Fs00268-014-2552-9>

332 Robicsek F (2004). Microfibrillar collagen hemostat in cardiac surgery, *J Thorac Cardiovasc Surg* 127(4):1228–, author reply 1228. <http://www.jtcvsonline.org/article/S0022-5223(04)00017-0/pdf>

333 Robicsek F, Masters TN, Littman L and Born GV (1981). The embolization of bone wax from sternotomy incisions, *The Annals of Thoracic Surgery* 31(4):357–359. <http://www.annalsthoracicsurgery.org/article/S0003-4975(10)60967-8/pdf>

334 Yang JC, Kim TW and Park KH (2013). Gelfoam-induced swallowing difficulty after anterior cervical spine surgery, *Korean Journal of Spine* 10(2):94–96. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3941718/pdf/kjs-10-94.pdf>

335 Vestergaard RF, Nielsen PH, Terp KA, S?balle K, Andersen G and Hasenkam JM (2014). Effect of hemostatic material on sternal healing after cardiac surgery, *The Annals of Thoracic Surgery* 97(1):153–160. <http://www.annalsthoracicsurgery.org/article/S0003-4975(13)01900-0/pdf>

336 Kazui T, Washiyama N, Bashar AH, Terada H, Suzuki K, Yamashita K, et al. (2001). Role of biologic glue repair of proximal aortic dissection in the development of early and midterm redissection of the aortic root, *The Annals of Thoracic Surgery* 72(2):509–514. <http://www.annalsthoracicsurgery.org/article/S0003-4975(01)02777-1/pdf>

337 Ngaage DL, Edwards WD, Bell MR and Sundt TM (2005). A cautionary note regarding long-term sequelae of biologic glue, *J Thorac Cardiovasc Surg* 129(4):937–938. <http://www.jtcvsonline.org/article/S0022-5223(04)01162-6/pdf>

338 Boodhwani M, Williams K, Babaev A, Gill G, Saleem N and Rubens FD (2006). Ultrafiltration reduces blood transfusions following cardiac surgery: A meta-analysis, *European Journal of Cardio-Thoracic Surgery* 30(6):892–897. <http://ejcts.oxfordjournals.org/content/30/6/892.full.pdf>

339 Golab HD, Scohy TV, de Jong PL, Takkenberg JJ and Bogers AJ (2008). Intraoperative cell salvage in infants undergoing elective cardiac surgery: a prospective trial, *European Journal of Cardio-Thoracic Surgery* 34(2):354–359. <http://ejcts.oxfordjournals.org/content/34/2/354.full.pdf>

340 Codispoti M and Mankad PS (2002). Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: randomised controlled trial, *European Journal of Cardio-Thoracic Surgery* 22(2):200–205. <http://ejcts.oxfordjournals.org/content/22/2/200.full.pdf>

341 Atkinson JB, Gomperts ED, Kang R, Lee M, Arensman RM, Bartlett RH, et al. (1997). Prospective, randomized evaluation of the efficacy of fibrin sealant as a topical hemostatic agent at the cannulation site in neonates undergoing extracorporeal membrane oxygenation, *American Journal of Surgery* 173(6):479–484. <http://www.americanjournalofsurgery.com/article/S0002-9610(97)00018-4/abstract>

342 CoStasis Multi-center Collaborative Writing C (2001). A novel collagen-based composite offers effective hemostasis for multiple surgical indications: Results of a randomized controlled trial, 129(4):445–450. <http://www.surgjournal.com/article/S0039-6060(01)81890-0/abstract>

343 Sirlak M, Eryilmaz S, Yazicioglu L, Kiziltepe U, Eyileten Z, Durdu MS, et al. (2003). Comparative study of microfibrillar collagen hemostat (Colgel) and oxidized cellulose (Surgicel) in high transfusion-risk cardiac surgery, *J Thorac Cardiovasc Surg* 126(3):666–670. <http://www.jtcvsonline.org/article/S0022-5223(03)00042-4/pdf>

344 Chapman WC, Singla N, Genyk Y, McNeil JW, Renkens KL, Reynolds TC, et al. (2007). A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis, *Journal of the American College of Surgeons* 205(2):256–265. <http://www.journalacs.org/article/S1072-7515(07)00456-5/abstract>

345 Weaver FA, Lew W, Granke K, Yonehiro L, Delange B, Alexander WA, et al. (2008). A comparison of recombinant thrombin to bovine thrombin as a hemostatic ancillary in patients undergoing peripheral arterial bypass and arteriovenous graft procedures, *Journal of Vascular Surgery* 47(6):1266–1273. <http://www.jvascsurg.org/article/S0741-5214(08)00106-7/pdf>

346 Lumsden AB, Heyman ER and Closure Medical Surgical Sealant Study G (2006). Prospective randomized study evaluating an absorbable cyanoacrylate for use in vascular reconstructions, *Journal of Vascular Surgery* 44(5):1002–1009, discussion 1009. <http://www.jvascsurg.org/article/S0741-5214(06)01213-4/pdf>

347 Oz MC, Cosgrove DM, Badduke BR, Hill JD, Flannery MR, Palumbo R, et al. (2000). Controlled clinical trial of a novel hemostatic agent in cardiac surgery, *The Annals of Thoracic Surgery* 69(5):1376–1382. <http://www.annalsthoracicsurgery.org/article/S0003-4975(00)01194-2/pdf>

348 Glickman M, Gheissari A, Money S, Martin J, Ballard JL and CoSeal Multicenter Vascular Surgery Study G (2002). A polymeric sealant inhibits anastomotic suture hole bleeding more rapidly than gelfoam/thrombin: results of a randomized controlled trial, *Archives of Surgery (Chicago, Ill.)* 137(3):326–331, discussion 332. <http://archsurg.jamanetwork.com/data/Journals/SURG/5348/soa1157.pdf>

349 Saha SP, Muluk S, Schenk W, Dennis JW, Ploder B, Grigorian A, et al. (2012). A prospective randomized study comparing fibrin sealant to manual compression for the treatment of anastomotic suture-hole bleeding in expanded polytetrafluoroethylene grafts, *Journal of Vascular Surgery* 56(1):134–141. <http://www.jvascsurg.org/article/S0741-5214(12)00077-8/pdf>

350 Nasso G, Piancone F, Bonifazi R, Romano V, Visicchio G, De Filippo CM, et al. (2009). Prospective, randomized clinical trial of the FloSeal matrix sealant in cardiac surgery, *The Annals of Thoracic Surgery* 88(5):1520–1526. <http://www.annalsthoracicsurgery.org/article/S0003-4975(09)01487-8/pdf>

351 Fischer CP, Bochicchio G, Shen J, Patel B, Batiller J and Hart JC (2013). A prospective, randomized, controlled trial of the efficacy and safety of fibrin pad as an adjunct to control soft tissue bleeding during abdominal, retroperitoneal, pelvic, and thoracic surgery, *Journal of the American College of Surgeons* 217(3):385–393. <http://www.journalacs.org/article/S1072-7515(13)00325-6/abstract>

352 Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, et al. (2011). 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines, *The Annals of Thoracic Surgery* 91(3):944–982. <http://www.annalsthoracicsurgery.org/article/S0003-4975(10)02888-2/pdf>

353 Barnard J and Millner R (2009). A review of topical hemostatic agents for use in cardiac surgery, *The Annals of Thoracic Surgery* 88(4):1377–1383. <http://www.annalsthoracicsurgery.org/article/S0003-4975(09)00382-8/pdf>

354 Achneck HE, Sileshi B, Jamiolkowski RM, Albala DM, Shapiro ML and Lawson JH (2010). A comprehensive review of topical hemostatic agents: efficacy and recommendations for use, *Annals of Surgery* 251(2):217–228.

355 Gabay M and Boucher BA (2013). An essential primer for understanding the role of topical hemostats, surgical sealants, and adhesives for maintaining hemostasis, *Pharmacotherapy* 33(9):935–955. <http://onlinelibrary.wiley.com/doi/10.1002/phar.1291/abstract>

356 Ozawa S (2013). Patient blood management: use of topical hemostatic and sealant agents, *AORN Journal* 98(5):461–478. <http://www.aornjournal.org/article/S0001-2092(13)00907-1/abstract>

357 WHO (2008). *Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia*, World Health Organization (WHO), Geneva. <http://whqlibdoc.who.int/publications/2008/9789241596657eng.pdf>

358 Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. (2014). A systematic analysis of global anemia burden from 1990 to 2010, *Blood* 123(5):615–624. <http://www.bloodjournal.org/content/123/5/615.long?sso-checked=true>

359 Domellof M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, et al. (2014). Iron requirements of infants and toddlers, 58(1):119–129.

360 Grant CC, Wall CR, Brewster D, Nicholson R, Whitehall J, Super L, et al. (2007). Policy statement on iron deficiency in pre-school-aged children, *J Paediatr Child Health* 43(7-8):513–521. <http://www.ncbi.nlm.nih.gov/pubmed/17635678>

361 European Society of Paediatric Gastroenterology Nutrition (1987). Nutrition and feeding of preterm infants. Committee on Nutrition of the Preterm Infant, European Society of Paediatric Gastroenterology and Nutrition, *Acta Paediatrica (Oslo, Norway). Supplement* 336:1–14.

362 Cormack B (2003). *Neonatal and Infant Nutrition Handbook*, Auckland District Health Board, Auckland.

363 NHMRC and MoH (2006). *Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes*, Australian National Health and Medical Research Council (NHMRC) and New Zealand Ministry of Health (MoH).

364 (2013). *Iron studies standardised reporting protocol*, Royal College of Pathologists of Australasia.

365 Ritchie B, McNeil Y and Brewster DR (2004). Soluble transferrin receptor in Aboriginal children with a high prevalence of iron deficiency and infection, *Tropical Medicine & International Health* 9(1):96–105. <http://onlinelibrary.wiley.com/store/10.1046/j.1365-3156.2003.01158.x/asset/j.1365-3156.2003.01158.x.pdf?v=1&t=iagfxhob&s=aeb4635832e92066da78409712e07e6d6a90810f>

366 Powers JM and Buchanan GR (2014). Diagnosis and management of iron deficiency anemia, *Hematol Oncol Clin North Am* 28(4):729–745, vi–vii. <http://www.ncbi.nlm.nih.gov/pubmed/25064710>

367 Gastroenterological Society of Australia (2008.). *Clinical update: Iron deficiency, First Edition*, Digestive Health Foundation, Sydney. <http://www.gesa.org.au>

368 Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, et al. (2010). Diagnosis and management of iron deficiency anaemia: a clinical update, *Med J Aust* 193(9):525–532. <http://www.ncbi.nlm.nih.gov/pubmed/21034387>

369 Goddard AF, James MW, McIntyre AS, Scott BB and British Society of G (2011). Guidelines for the management of iron deficiency anaemia, *Gut* 60(10):1309–1316. <http://gut.bmj.com/content/60/10/1309.full.pdf>

370 *Point-of-care quick reference: Iron deficiency anemia*, American Academy of Pediatrics. <http://pediatriccare.solutions.aap.org/Content.aspx?gbosid=165534>

371 Paediatric Pharmacopoiea (2002). *Pocket prescriber (13th Edition)*, 13th ed, Pharmacy Department, The Royal Children's Hospital.

372 Crary SE, Hall K and Buchanan GR (2011). Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy, *Pediatr Blood Cancer* 56(4):615–619. <http://onlinelibrary.wiley.com/doi/10.1002/pbc.22930/abstract>

373 Laass MW, Straub S, Chainey S, Virgin G and Cushway T (2014). Effectiveness and safety of ferric carboxymaltose treatment in children and adolescents with inflammatory bowel disease and other gastrointestinal diseases, *BMC Gastroenterol* 14:184. <http://www.ncbi.nlm.nih.gov/pubmed/25326048>

374 Pinsk V, Levy J, Moser A, Yerushalmi B and Kapelushnik J (2008). Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia, *The Israel Medical Association Journal* 10(5):335–338.

375 Tenenbein M and Rodgers GC (1994). The four A's of decreasing the toll of childhood iron poisoning deaths, *Archives of Family Medicine* 3(9):754–755.

376 Hendrickson JE, Shaz BH, Pereira G, Atkins E, Johnson KK, Bao G, et al. (2012). Coagulopathy is prevalent and associated with adverse outcomes in transfused pediatric trauma patients, *J Pediatr* 160(2):204–209 e203. <http://www.ncbi.nlm.nih.gov/pubmed/21925679>

377 Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, et al. (2012). Implementation of a pediatric trauma massive transfusion protocol: one institution's experience, *Transfusion* 52(6):1228–1236. <http://www.ncbi.nlm.nih.gov/pubmed/22128884>

378 Chidester SJ, Williams N, Wang W and Groner JI (2012). A pediatric massive transfusion protocol, *J Trauma Acute Care Surg* 73(5):1273–1277. <http://www.ncbi.nlm.nih.gov/pubmed/23064608>

379 Dressler AM, Finck CM, Carroll CL, Bonanni CC and Spinella PC (2010). Use of a massive transfusion protocol with hemostatic resuscitation for severe intraoperative bleeding in a child, *J Pediatr Surg* 45(7):1530–1533. <http://www.ncbi.nlm.nih.gov/pubmed/20638538>

380 Diab YA, Wong EC and Luban NL (2013). Massive transfusion in children and neonates, *Br J Haematol* 161(1):15–26. <http://www.ncbi.nlm.nih.gov/pubmed/23432321>

381 (2015). *Transfusion of Prematures (TOP) Trial*. <https://clinicaltrials.gov/ct2/show/NCT01702805>

382 <ETTNO\_Information\_HomepageCPCS\_AF.pdf>.

383 (2013). *National Patient Blood Management Guidelines Implementation Strategy 2013–17* National Blood Authority, Canberra. <http://www.blood.gov.au/implementing-pbm>

384 Australian Council on Healthcare Standards (2013). *National Safety and Quality Health Service (NSQHS) Standards*. <http://www.safetyandquality.gov.au/our-work/accreditation-and-the-nsqhs-standards/resources-to-implement-the-nsqhs-standards/#NSQHS-Standards>

385 (2013). *National Blood Sector Education and Training Strategy 2013–2016*, National Blood Authority, Canberra. <http://www.blood.gov.au/education-and-training>

386 (2011). *National Safety and Quality Health Service Standards*, Australian Commission on Safety and Quality in Health Care, Sydney. <http://www.safetyandquality.gov.au/wp-content/uploads/2011/09/NSQHS-Standards-Sept-2012.pdf>

387 Snyder-Ramos SA, Mohnle P, Weng YS, Bottiger BW, Kulier A, Levin J, et al. (2008). The ongoing variability in blood transfusion practices in cardiac surgery, *Transfusion* 48(7):1284–1299. <http://www.ncbi.nlm.nih.gov/pubmed/18422857>

388 National Blood Authority (NBA) (In preparation). *Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity: Technical Report Volume 1 – Appendixes*, NBA, Canberra, Australia.

389 National Blood Authority (NBA) (In preparation). *Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity: Technical Report Volume 2 – Annexes*, NBA, Canberra, Australia.

390 Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. (2010). AGREE II: advancing guideline development, reporting and evaluation in health care, *CMAJ* 182(18):E839-842. <http://www.ncbi.nlm.nih.gov/pubmed/20603348>

391 Calman K (1996). The health of the nation, *British Journal of Hospital Medicine* 56(4):125–126. <http://www.ncbi.nlm.nih.gov/pubmed/8872334>

392 (2003). *National Blood Agrreement*, Canberra.

393 Guillen U, Cummings JJ, Bell EF, Hosono S, Frantz AR, Maier RF, et al. (2012). International survey of transfusion practices for extremely premature infants, *Semin Perinatol* 36(4):244–247. <http://www.ncbi.nlm.nih.gov/pubmed/22818544>

394 Blanchette VS and Zipursky A (1984). Assessment of anemia in newborn infants, *Clin Perinatol* 11(2):489–510. <http://www.ncbi.nlm.nih.gov/pubmed/6378489>

395 RCPCH (2012). *Major trauma and the use of tranexamic acid in children*, Royal College of Paediatrics and Child Health. <http://www.rcpch.ac.uk/improving-child-health/quality-improvement-and-clinical-audit/childrens-medicines/childrens-medicine#TXA>

396 (2013). *Day Medical Unit – Treatment protocol: Administration of iron carboxymaltose (Ferinject);Version 4*, Royal Children's Hospital, Melbourne, Australia.

397 (2012). *Day Medical Unit – Treatment protocol: Administration of iron sucrose (Venofer)*, Royal Children's Hospital, Melbourne, Australia.

398 (2012). *Day Medical Unit – Treatment protocol: Administration of iron polymaltose (Ferrosig)*, Royal Children's Hospital, Melbourne, Australia.

399 Luban NLC (2012). Transfusion of blood and blood products, In MacDonald M, Ramasethu J, et al. (eds.), *Atlas of procedures in neonatology, Fifth edition* Wolters Kluwer/Lippincott Williams & Wilkins.

400 Davies P, Robertson S, Hegde S, Greenwood R, Massey E and Davis P (2007). Calculating the required transfusion volume in children, *Transfusion* 47(2):212–216. <http://www.ncbi.nlm.nih.gov/pubmed/17302766>

401 Morris KP, Naqvi N, Davies P, Smith M and Lee PW (2005). A new formula for blood transfusion volume in the critically ill, *Arch Dis Child* 90(7):724–728. <http://www.ncbi.nlm.nih.gov/pubmed/15970617>

1. The structure of the Australian blood sector is outlined in Appendix D [↑](#footnote-ref-1)
2. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-2)
3. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-3)
4. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-4)
5. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-5)
6. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-6)
7. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-7)
8. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-8)
9. Premature and low birth weight infants are covered in the previous section [↑](#footnote-ref-9)
10. This evidence has not undergone a strict systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes); therefore, these results should be interpreted with caution. [↑](#footnote-ref-10)
11. The Jurisdictional Blood Committee (JBC) recently approved the addition of fibrinogen concentrate for patients with congenital fibrinogen deficiency to the list of products funded and supplied under the national blood arrangements administered by the NBA. Fibrinogen concentrate became available for treatment of congenital fibrinogen deficiency under the NBA arrangements from 1 July 2014. [↑](#footnote-ref-11)
12. Cryoprecipitate and fibrinogen concentrate are therapeutic interventions used in the correction of low fibrinogen levels. [↑](#footnote-ref-12)
13. The Jurisdictional Blood Committee (JBC) recently approved the addition of fibrinogen concentrate for patients with congenital fibrinogen deficiency to the list of products funded and supplied under the national blood arrangements administered by the NBA. Fibrinogen concentrate became available for treatment of congenital fibrinogen deficiency under the NBA arrangements from 1 July 2014. [↑](#footnote-ref-13)
14. For this module, cultural safety is defined as the ‘effective (health care) of a person/family from another culture by a (health professional) who has undertaken a process of reflection on (their) own cultural identity and (that) recognises the impact of the (health professional’s) culture on their own (health professional’s) practice’. Unsafe cultural practice is defined as ‘any action which diminishes, demeans or disempowers the cultural identity and wellbeing of an individual’[216](#_ENREF_216) (p.6). The terminology as well as the meaning of culturally secure care is extensively described in the literature[217-225](#_ENREF_217) and can be confusing for the non-expert. [↑](#footnote-ref-14)
15. CRANA Plus is a professional organisation representing Australian rural and remote nurses and midwives (see <https://crana.org.au/>) [↑](#footnote-ref-15)
16. This is a draft list that has been adapted and reproduced here with permission. [↑](#footnote-ref-16)
17. The PCC available in Australia is produced by CSL Limited, and distributed by the Australian Red Cross Blood Service. [↑](#footnote-ref-17)
18. Adapted from Box 3.1 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[2](#_ENREF_2) [↑](#footnote-ref-18)
19. The Phase III TWiTCH trial comparing RBC transfusion to hydroxyurea in paediatric sickle cell patients was stopped early because hydroxyurea was found to be as effective as transfusions in lowering the mean TCD velocity of blood flow. Complete data, including the secondary outcome of primary stroke, are not available. We await publication of the full trial results before a reassessment of the current recommendations (R1 and R4) and practice points (PP11) are made. [↑](#footnote-ref-19)
20. http://www.blood.gov.au/ [↑](#footnote-ref-20)
21. http://www.blood.gov.au/ [↑](#footnote-ref-21)
22. http://www.transfusion.com.au/blood\_products/components/red\_cells [↑](#footnote-ref-22)